

The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the sulfonamide (0.50 g, 80%, GS 273805) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.0 (d, J = 1.5 Hz, 1H), 8.8 (dd, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.48 (m, 1H), 7.36 (m, 10H), 7.12 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.18 (m, 4H), 5.06 (m, 1H), 4.93 (d, 1H), 4.21 (d, J = 8.4 Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.74 (m, 2H), 3.2 (m, 1H), 3.1-2.83 (m, 5H), 2.76 (m, 1H), 1.88 (m, 1H), 1.62 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.3.

#### Example M17

Phosphonic Acid 17: To a solution of 16 (40 mg, 0.049 mmol) in MeOH (3 mL) and AcOH (1 mL) was added 10% Pd/C (10 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (28 mg, 90%, GS 273845) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.98 (s, 1H), 8.77 (broad, s, 1H), 8.25 (dd, 1H), 7.6 (m, 1H), 7.15 (m, 2H), 6.90 (m, 2H), 5.6 (d, J = 5.4 Hz, 1H), 4.98 (m, 1H), 4.15 (d, 2H), 3.97-3.7 (m, 6H), 3.45-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.9 (m, 6H).

#### Example M18

Sulfonamide 18: A solution of dibenzylphosphonate 6 (0.15 g, 0.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.60 mL) at 0°C was treated with trifluoroacetic acid (0.30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and cooled to 0°C. Triethylamine (0.11 mL, 0.76 mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (43 mg, 0.21 mmol). The solution was stirred for 30 min at 0°C and warmed to room temperature for 30 min. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the sulfonamide (0.13 g, 80%, GS 278114) as a white solid: <sup>1</sup>H NMR

(CDCl<sub>3</sub>)  $\delta$  10.1 (s, 1H), 8.04 (d,  $J$  = 8.1 Hz, 2H), 7.94 (d,  $J$  = 8.1 Hz, 2H), 7.35 (m, 10H), 7.13 (m,  $J$  = 8.1 Hz, 2H), 6.82 (d,  $J$  = 8.1 Hz, 2H), 5.65 (d,  $J$  = 5.4 Hz, 1H), 5.17 (m, 4H), 5.06 (m, 1H), 4.93 (m, 1H), 4.2 (d,  $J$  = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.18-2.87 (m, 5H), 2.78 (m, 1H), 1.86 (m, 1H), 1.67-1.58 (m, 2H), 0.93 (d,  $J$  = 6.6 Hz, 3H), 0.88 (d,  $J$  = 6.6 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  20.3.

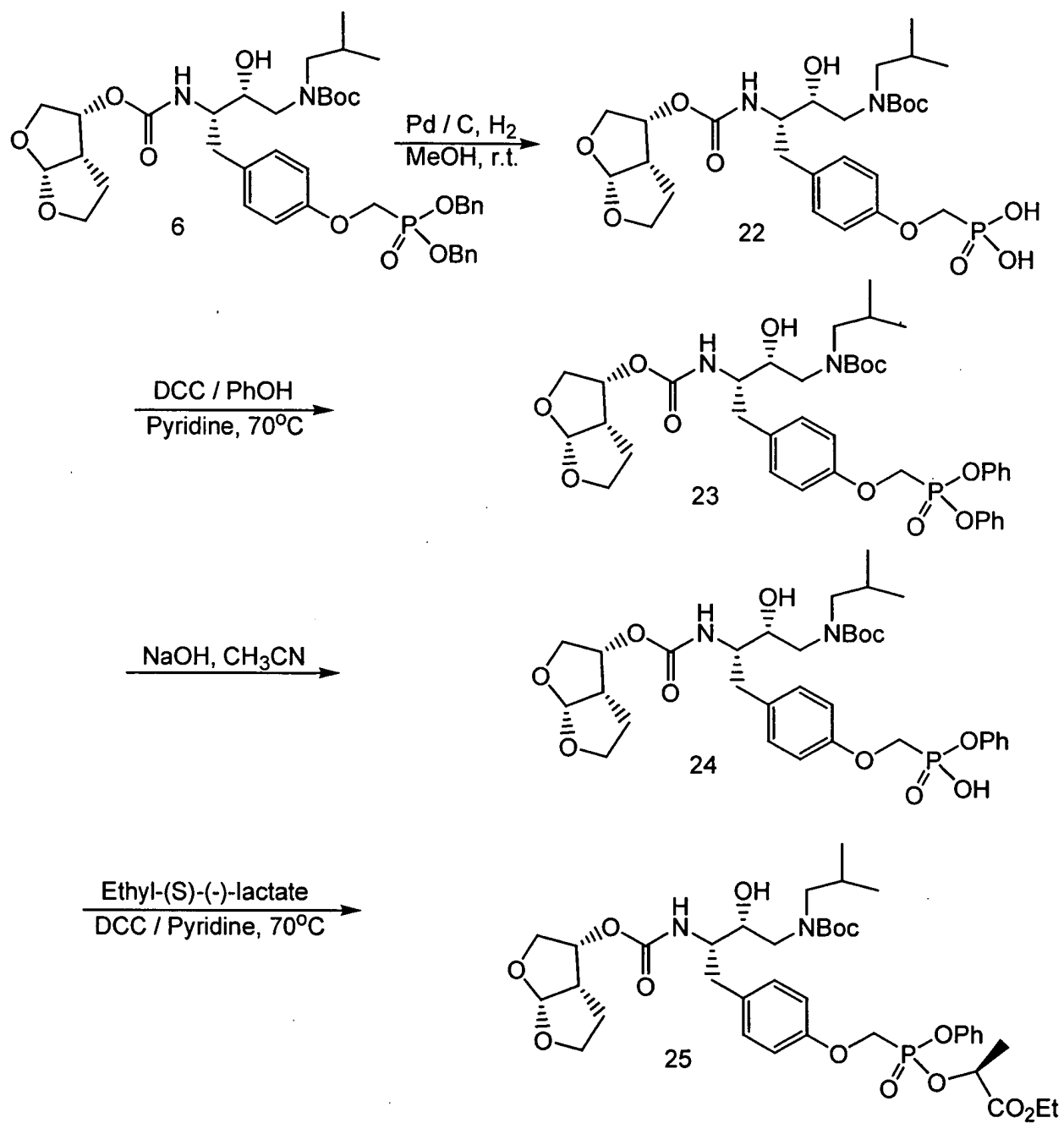
#### Example M19

Phosphonic Acid 19: To a solution of 18 (0.12 g, 0.15 mmol) in EtOAc (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (93 mg, 95%) as a white solid.

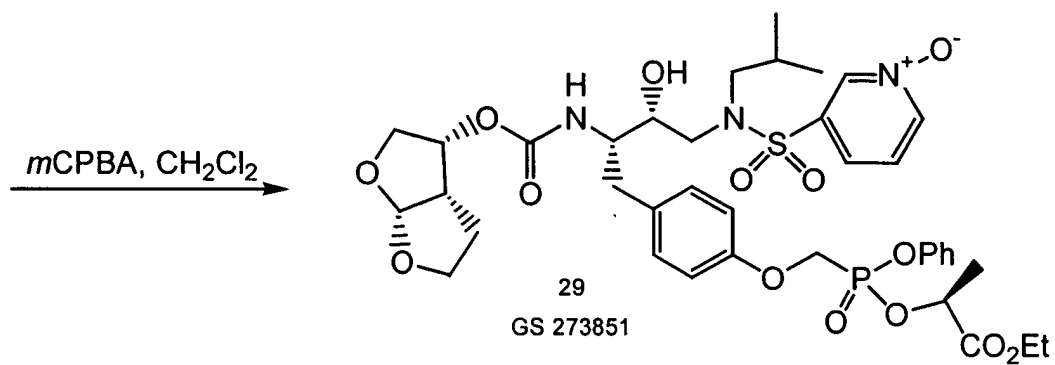
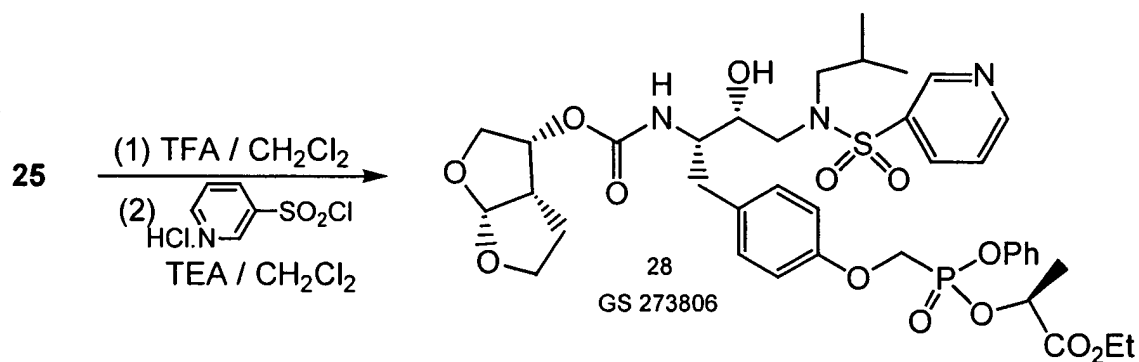
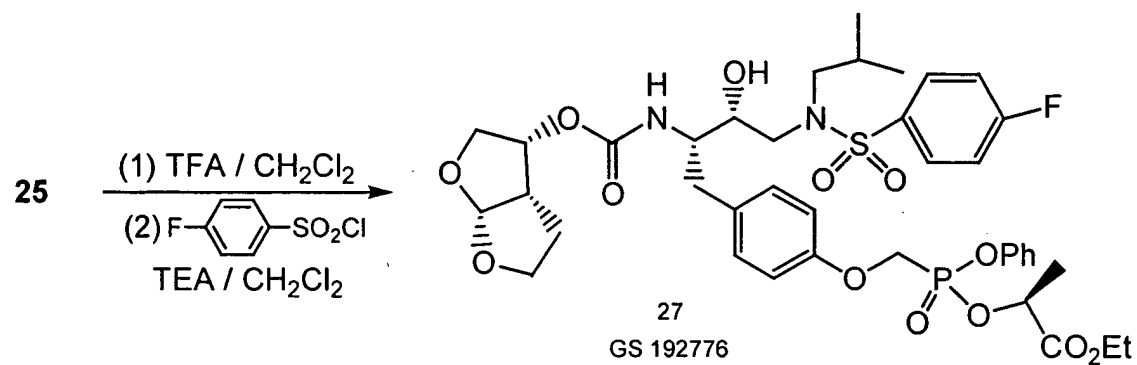
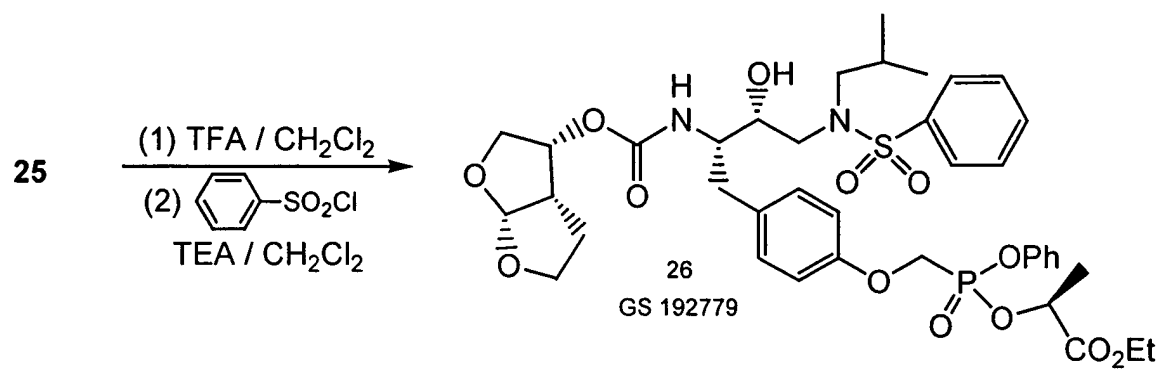
#### Example M20

Phosphonic Acids 20 and 21: Compound 19 (93 mg, 0.14 mmol) was dissolved in CH<sub>3</sub>CN (2 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.28 g, 1.4 mmol) was added. The reaction mixture was heated to reflux for 1 h, cooled to room temperature and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a semi-solid which was dissolved in EtOAc (2 mL). Morpholine (60  $\mu$ L, 0.9 mmol), AcOH (32  $\mu$ L, 0.56 mmol), and NaBH<sub>3</sub>CN (17 mg, 0.28 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with H<sub>2</sub>O, stirred for 2 h, filtered, and concentrated. The crude product was purified by HPLC to give the phosphonic acid 20 (10 mg, GS 278118) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.80 (d,  $J$  = 7.8 Hz, 2H), 7.56 (d,  $J$  = 7.5 Hz, 2H), 7.17 (d,  $J$  = 7.8 Hz, 2H), 6.91 (d,  $J$  = 7.5 Hz, 2H), 5.59 (d,  $J$  = 5.1 Hz, 1H), 5.06 (m, 1H), 4.7 (s, 2H), 4.15 (d,  $J$  = 10.2 Hz, 2H), 3.92 (m, 1H), 3.82-3.7 (m, 5H), 3.43 (dd, 1H), 3.11-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD)  $\delta$  17.3. Phosphonic acid 21 (15 mg, GS 278117) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.8-7.7 (m, 4H), 7.20 (d,  $J$  = 8.4 Hz, 2H), 6.95 (d,  $J$  = 8.4 Hz, 2H), 5.62 (d,  $J$  = 5.1 Hz, 1H), 5.00 (m, 1H), 4.42 (s, 2H), 4.20 (dd, 2H), 3.98-3.68 (m, 9H), 3.3-2.92 (m, 11H), 2.6 (m, 1H), 2.0 (m, 1H), 1.6 (m, 2H), 0.92 (d,  $J$  = 6.6 Hz, 3H), 0.88 (d,  $J$  = 6.6 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD)  $\delta$  16.2.

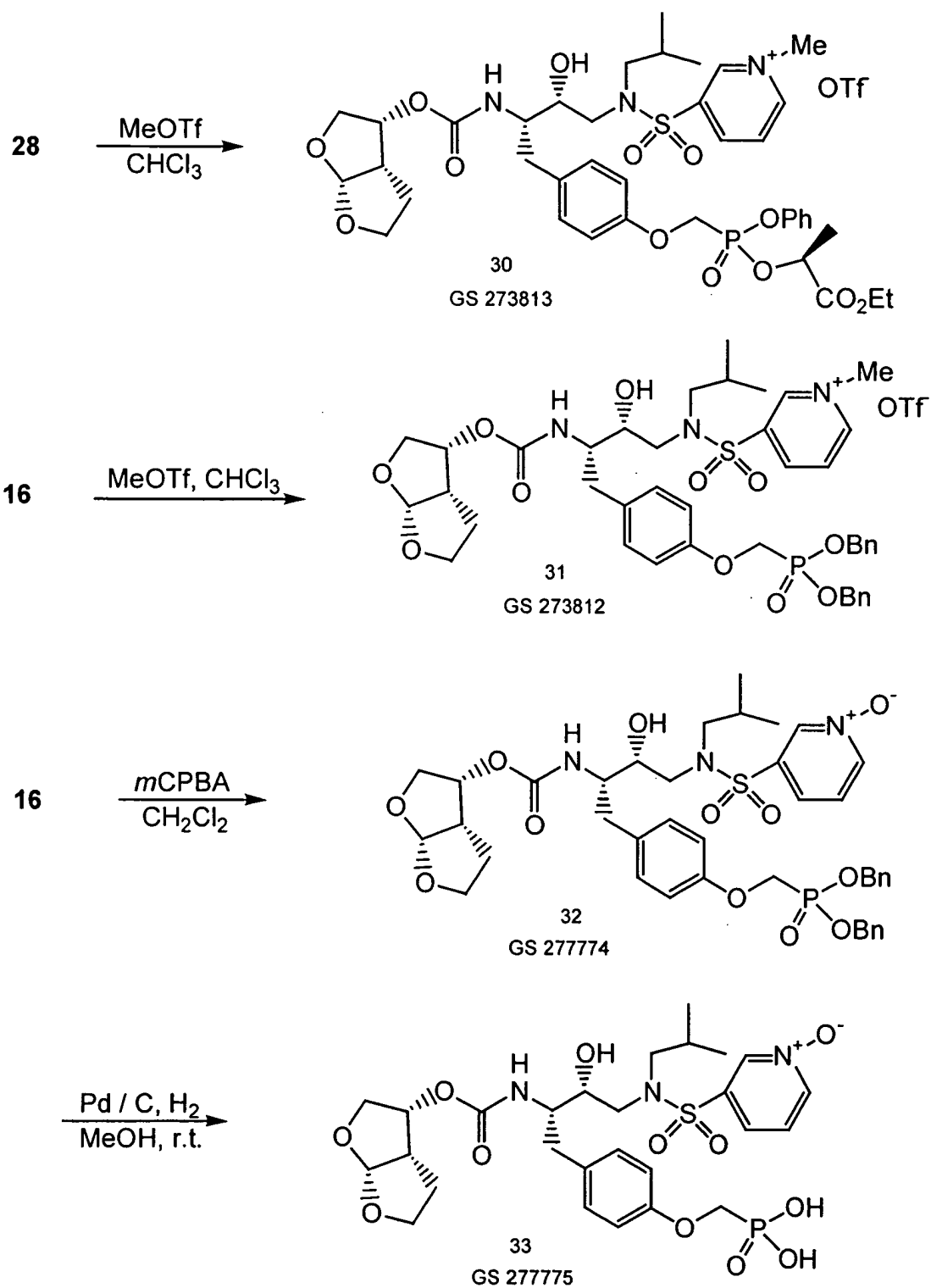
**Scheme M6**



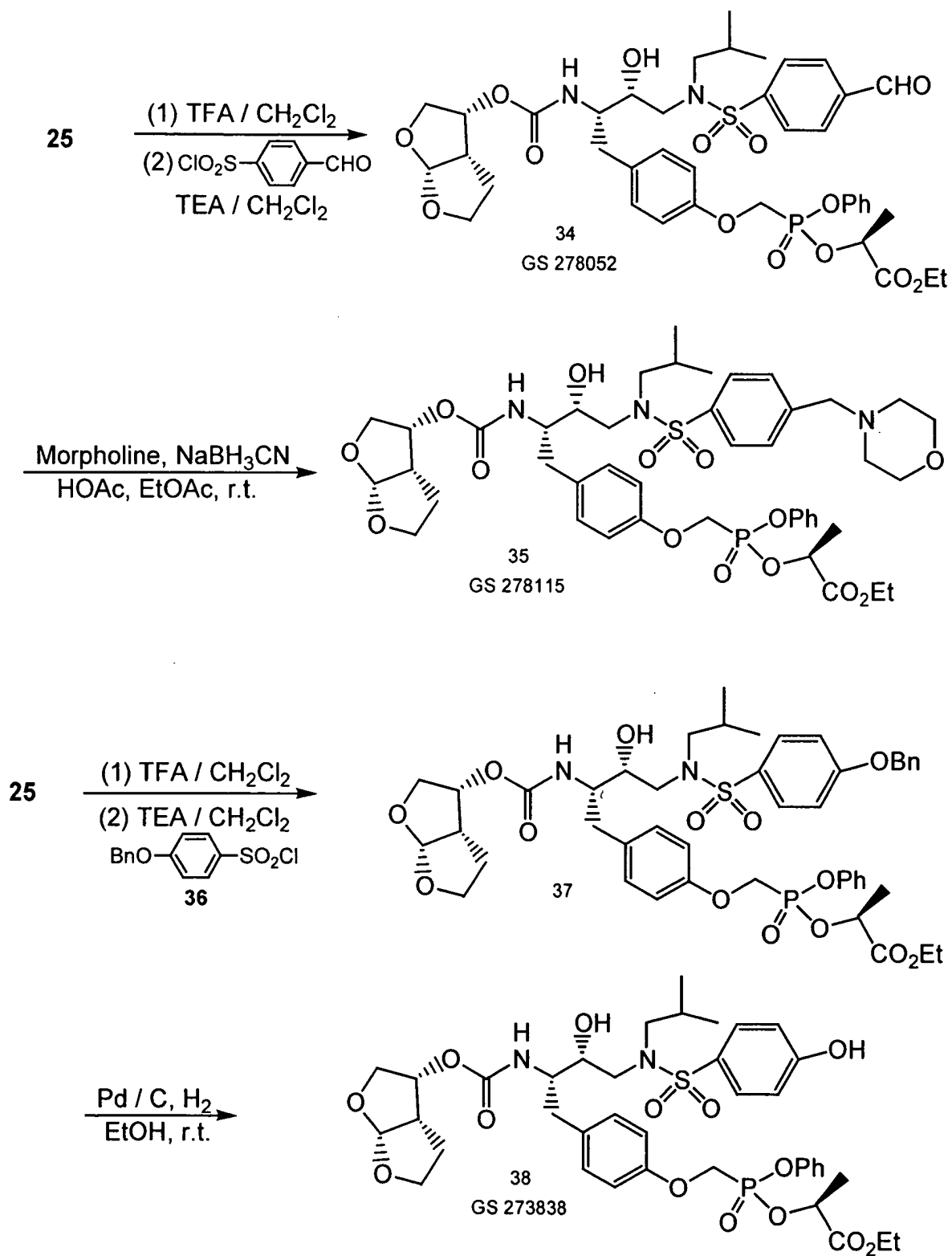
Scheme M7



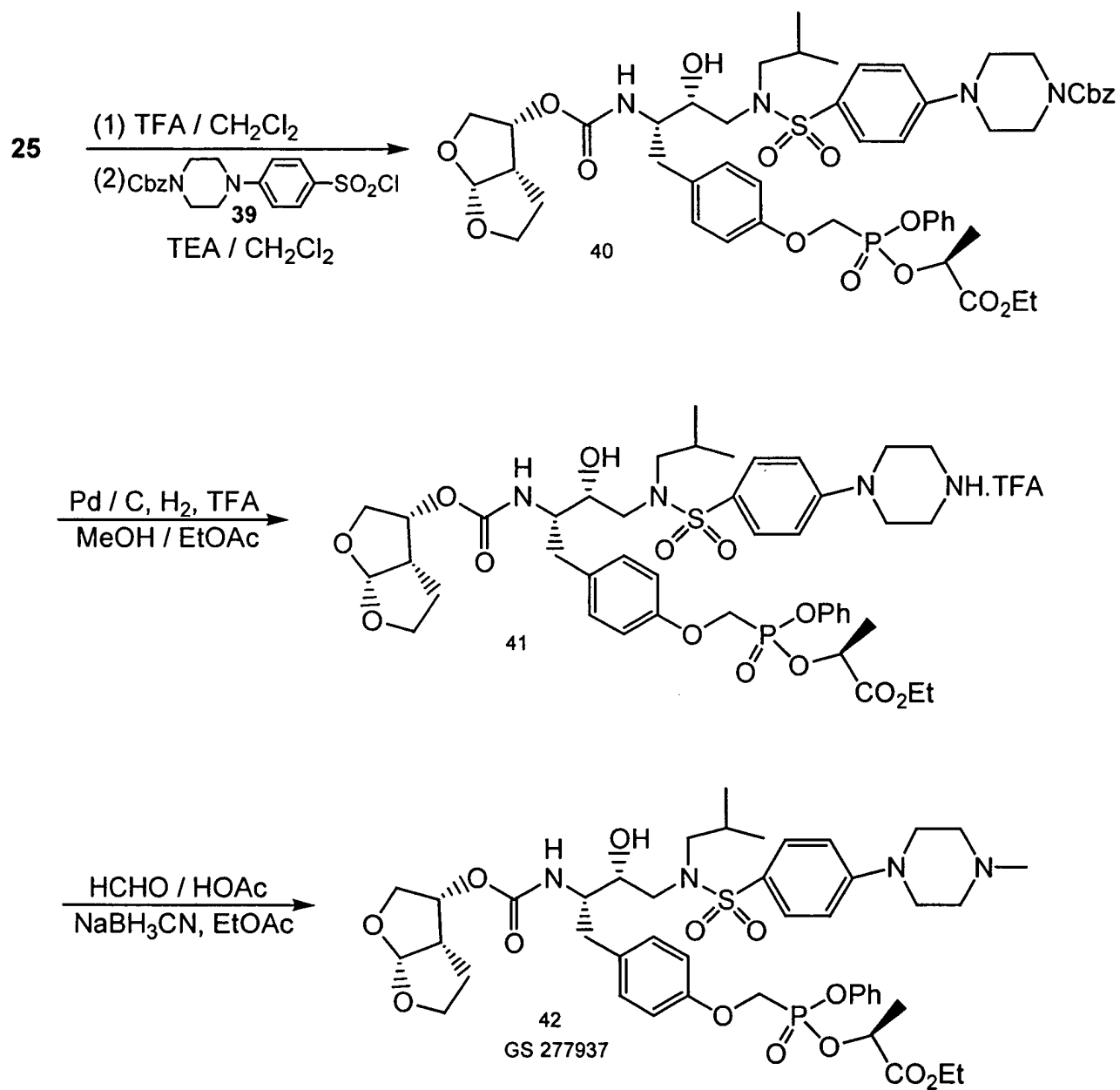
Scheme M8



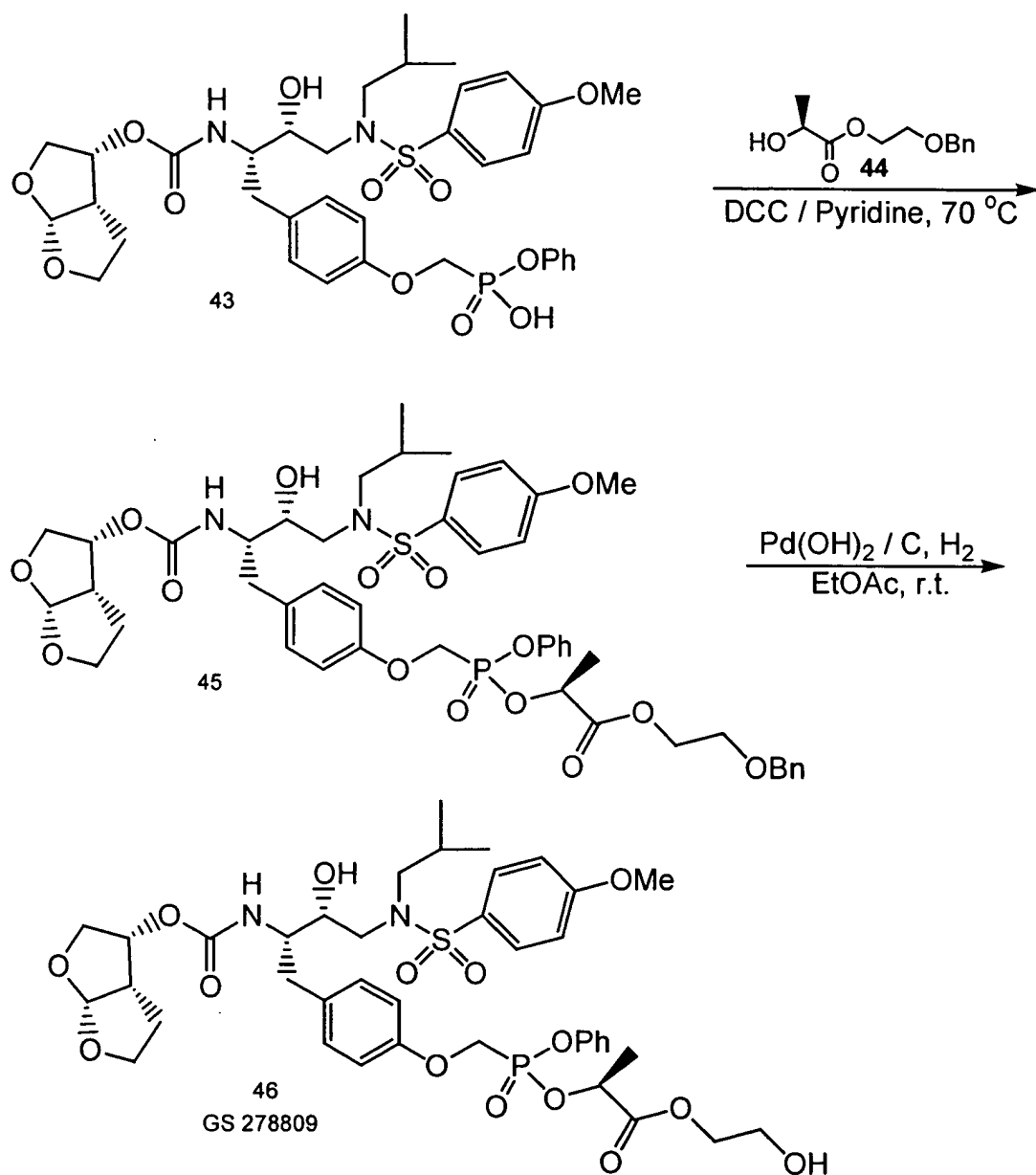
Scheme M9



**Scheme M10**



### Scheme M11



### Example M21

Phosphonic Acid 22: To a solution of dibenzylphosphonate 6 (5.00 g, 6.39 mmol) in EtOH (100 mL) was added 10% Pd/C (1.4 g). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (3.66 g, 95%) as a white solid.

#### Example M22

Diphenylphosphonate 23: A solution of 22 (3.65 g, 6.06 mmol) and phenol (5.70 g, 60.6 mmol) in pyridine (30 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (5.00 g, 24.24 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH<sub>3</sub>CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the diphenylphosphonate (2.74 g, 60%) as a white solid.

#### Example M23

Monophosphonic Acid 24: To a solution of 23 (2.74 g, 3.63 mmol) in CH<sub>3</sub>CN (40 mL) at 0°C was added 1 N NaOH (9.07 mL, 9.07 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.34 g, 95%) as a white solid.

#### Example M24

Monophospholactate 25: A solution of 24 (2.00 g, 2.95 mmol) and ethyl-(S)-(-)-lactate (1.34 mL, 11.80 mmol) in pyridine (20 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.43 g, 11.80 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (1.38 g, 60%) as a white solid.

### Example M25

Monophospholactate 26: A solution of 25 (0.37 g, 0.48 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.80 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.40 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.27 mL, 1.92 mmol) was added followed by the treatment of benzenesulfonyl chloride (84 mg, 0.48 mmol). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.2 N HCl. The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.33 g, 85%, GS 192779, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.78 (dd, 2H), 7.59 (m, 3H), 7.38-7.18 (m, 7H), 6.93 (dd, 2H), 5.66 (m, 1H), 5.18-4.93 (m, 3H), 4.56-4.4 (m, 2H), 4.2 (m, 2H), 4.1-3.7 (m, 6H), 3.17 (m, 1H), 3.02-2.8 (m, 6H), 1.84 (m, 1H), 1.82-1.5 (m, 5H), 1.27 (m, 3H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4, 15.3.

### Example M26

Monophospholactate 27: A solution of 25 (0.50 g, 0.64 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.36 mL, 2.56 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (0.13 g, 0.64 mmol). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.2 N HCl. The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.44 g, 81%, GS 192776, 3/2 diastereomeric mixture) as a white solid:

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.80 (m, 2H), 7.38-7.15 (m, 9H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-4.9 (m, 3H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.1-3.7 (m, 6H), 3.6 (broad, s, 1H), 3.17 (m, 1H), 3.02-2.75 (m, 6H), 1.85 (m, 1H), 1.7-1.5 (m, 5H), 1.26 (m, 3H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.2.

#### Example M27

Monophospholactate 28: A solution of 25 (0.50 g, 0.64 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.45 mL, 3.20 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinylsulfonyl chloride (0.14 g, 0.65 mmol). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.41 g, 79%, GS 273806, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.0 (s, 1H), 8.83 (dd, 1H), 8.06 (d,  $J = 7.8$  Hz, 1H), 7.5 (m, 1H), 7.38-7.15 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.18-4.95 (m, 3H), 4.6-4.41 (m, 2H), 4.2 (m, 2H), 4.0 (m, 1H), 3.95-3.76 (m, 6H), 3.23-2.8 (m, 7H), 1.88 (m, 1H), 1.7-1.5 (m, 5H), 1.26 (m, 3H), 0.93 (d,  $J = 6.6$  Hz, 3H), 0.83 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.3.

#### Example M28

Monophospholactate 29: A solution of compound 28 (0.82 g, 1.00 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) at  $0^\circ\text{C}$  was treated with *m*CPBA (1.25 eq). The solution was stirred for 1 h at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 6 h. The reaction mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.59 g, 70%, GS 273851, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$

NMR (CDCl<sub>3</sub>)  $\delta$  8.63 (dd, 1H), 8.3 (dd, 1H), 7.57 (m, 1H), 7.44 (m, 1H), 7.38-7.13 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-5.05 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.0-3.73 (m, 6H), 3.2 (m, 2H), 3.0 (m, 4H), 2.77 (m, 1H), 1.92 (m, 1H), 1.7-1.49 (m, 5H), 1.26 (m, 3H), 0.91 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  17.3, 15.3.

#### Example M29

Monophospholactate 30: A solution of compound 28 (71 mg, 0.087 mmol) in CHCl<sub>3</sub> (1 mL) was treated with MeOTf (18 mg, 0.11 mmol). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated and co-evaporated with toluene (2 x), CHCl<sub>3</sub> (2 x) and dried under vacuum to give the monophospholactate (81 mg, 95%, GS 273813, 1:1 diastereomeric mixture ) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.0 (dd, 1H), 8.76 (m, 2H), 8.1 (m, 1H), 7.35-7.1 (m, 7H), 6.89 (m, 2H), 5.64 (m, 1H), 5.25-5.0 (m, 3H), 4.6-4.41 (m, 5H), 4.2 (m, 2H), 3.92-3.72 (m, 6H), 3.28 (m, 2H), 3.04-2.85 (m, 3H), 2.62 (m, 1H), 1.97 (m, 1H), 1.62-1.5 (m, 5H), 1.25 (m, 3H), 0.97 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  17.4, 15.4.

#### Example M30

Dibenzylphosphonate 31: A solution of compound 16 (0.15 g, 0.18 mmol) in CHCl<sub>3</sub> (2 mL) was treated with MeOTf (37 mg, 0.23 mmol). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and co-evaporated with toluene (2 x), CHCl<sub>3</sub> (2 x) and dried under vacuum to give the dibenzylphosphonate (0.17 g, 95%, GS 273812) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.0 (dd, 1H), 8.73 (m, 2H), 8.09 (m, 1H), 7.35 (m, 10H), 7.09 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.1 Hz, 2H), 5.61 (d, J = 4.2 Hz, 1H), 5.2-4.96 (m, 6H), 4.54 (s, 3H), 4.2 (dd, 2H), 3.92-3.69 (m, 6H), 3.3 (m, 2H), 3.04-2.6 (m, 5H), 1.97 (m, 1H), 1.6 (m, 2H), 0.98 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  20.4.

#### Example M31

Dibenzylphosphonate 32: A solution of compound 16 (0.15 g, 0.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) at 0°C was treated with *m*CPBA (1.25 eq). The solution was stirred for 1 h at 0°C and then warmed to room temperature overnight. The reaction mixture was partitioned between 10% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the

dibenzylphosphonate (0.11 g, 70%, **GS 277774**) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.64 (m, 1H), 8.27 (d,  $J$  = 6.9 Hz, 1H), 7.57 (d,  $J$  = 8.4 Hz, 1H), 7.36 (m, 11H), 7.10 (d,  $J$  = 8.4 Hz, 2H), 6.81 (d,  $J$  = 8.7 Hz, 2H), 5.65 (d,  $J$  = 5.4 Hz, 1H), 5.22-5.02 (m, 6H), 4.21 (dd, 2H), 3.99-3.65 (m, 6H), 3.2 (m, 2H), 3.03-2.73 (m, 5H), 1.90 (m, 1H), 1.66-1.56 (m, 2H), 0.91 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3.

#### Example M32

Phosphonic Acid 33: To a solution of dibenzylphosphonate 32 (0.1 g, 0.12 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 1 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and purified by HPLC to give the phosphonic acid (17 mg, **GS 277775**) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.68 (s, 1H), 8.47 (d,  $J$  = 6.0 Hz, 1H), 7.92 (d,  $J$  = 7.8 Hz, 1H), 7.68 (m, 1H), 7.14 (m, 2H), 6.90 (d,  $J$  = 7.8 Hz, 2H), 5.58 (d,  $J$  = 5.4 Hz, 1H), 5.00 (m, 1H), 4.08 (d,  $J$  = 9.9 Hz, 2H), 3.93-3.69 (m, 6H), 3.4-2.9 (m, 7H), 2.5 (m, 1H), 2.04 (m, 1H), 1.6-1.35 (m, 2H), 0.92 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  15.8.

#### Example M33

Monophospholactate 34: A solution of 25 (2.50 g, 3.21 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (2.5 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (30 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (1.79 mL, 12.84 mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (0.72 g, 3.53 mmol) and the solution was stirred at  $0^\circ\text{C}$  for 1 h. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 5% HCl. The organic phase was washed with  $\text{H}_2\text{O}$ , saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (2.11 g, 77%, **GS 278052**, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  10.12 (s, 1H), 8.05 (d,  $J$  = 8.7 Hz, 2H), 7.95 (d,  $J$  = 7.5 Hz, 2H), 7.38-7.15 (m, 7H), 6.94 (m, 2H), 5.67 (m, 1H), 5.18-4.91 (m, 3H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.0-3.69 (m, 6H), 3.57 (broad, s, 1H), 3.19-2.8 (m, 7H), 1.87

(m, 1H), 1.69-1.48 (m, 5H), 1.25 (m, 3H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.2.

#### Example M34

Monophospholactate 35: A solution of 34 (0.60 g, 0.71 mmol) and morpholine (0.31 mL, 3.54 mmol) in EtOAc (8 mL) was treated with HOAc (0.16 mL, 2.83 mmol) and  $\text{NaBH}_3\text{CN}$  (89 mg, 1.42 mmol). The reaction mixture was stirred at room temperature for 4 h. The product was partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic phase was washed with brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.46 g, 70%, GS 278115, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 8.4$  Hz, 2H), 7.52 (d,  $J = 8.4$  Hz, 2H), 7.38-7.15 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-5.0 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 3.97-3.57 (m, 12H), 3.2-2.78 (m, 7H), 2.46 (broad, s, 4H), 1.87 (m, 1H), 1.64-1.5 (m, 5H), 1.25 (m, 3H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.3.

#### Example M35

Monophospholactate 37: A solution of 25 (0.50 g, 0.64 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (1 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.45 mL, 3.20 mmol) was added followed by the treatment of 4-benzyloxybenzenesulfonyl chloride (0.18 g, 0.64 mmol, prepared according to Toja, E. *et al.* *Eur. J. Med. Chem.* 1991, 26, 403). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.51 g, 85%) as a white solid.

### Example M36

Monophospholactate 38: To a solution of 37 (0.48 g, 0.52 mmol) in EtOH (15 mL) was added 10% Pd/C (0.10 g). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.38 g, 88%, GS 273838, 1:1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.86 (dd, 1H), 7.42-7.25 (m, 9H), 6.91 (m, 4H), 5.73 (d, J = 5.1 Hz, 1H), 5.42 (m, 1H), 5.18 (m, 2H), 4.76-4.31 (m, 2H), 4.22 (m, 2H), 4.12-3.75 (m, 6H), 3.63 (broad, s, 1H), 3.13 (m, 3H), 2.87 (m, 1H), 2.63 (m, 1H), 2.4 (m, 1H), 2.05 (m, 2H), 1.9 (m, 1H), 1.8 (m, 1H), 1.6 (m, 3H), 1.25 (m, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.1, 15.7.

### Example M37

Monophospholactate 40: A solution of 25 (0.75 g, 0.96 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at 0°C was treated with trifluoroacetic acid (1 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and cooled to 0°C. Triethylamine (0.67 mL, 4.80 mmol) was added followed by the treatment of 4-(4'-benzyloxycarbonyl piperazinyl)benzenesulfonyl chloride (0.48 g, 1.22 mmol, prepared according to Toja, E. *et al.* *Arzneim. Forsch.* 1994, 44, 501). The solution was stirred at 0°C for 1 h and then warmed to room temperature for 30 min. The product was partitioned between 10% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub> and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.63 g, 60%) as a white solid.

### Example M38

Monophospholactate 41: To a solution of 40 (0.62 g, 0.60 mmol) in MeOH (8 mL) and EtOAc (2 mL) was added 10% Pd/C (0.20 g). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of

celite. The filtrate was treated with 1.2 equivalent of TFA, co-evaporated with  $\text{CHCl}_3$  and dried under vacuum to give the monophospholactate (0.55 g, 90%) as a white solid.

#### Example M39

Monophospholactate 42: A solution of 41 (0.54 g, 0.53 mmol) and formaldehyde (0.16 mL, 5.30 mmol) in EtOAc (10 mL) was treated with HOAc (0.30 mL, 5.30 mmol) and  $\text{NaBH}_3\text{CN}$  (0.33 g, 5.30 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic phase was washed with brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (97.2 mg, 20%, GS 277937, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.64 (d,  $J$  = 9.0 Hz, 2H), 7.38-7.17 (m, 7H), 6.95-6.88 (m, 4H), 5.67 (m, 1H), 5.2-4.96 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 3.97-3.64 (m, 8H), 3.49-3.37 (m, 4H), 3.05-2.78 (m, 12H), 1.88-1.62 (m, 3H), 1.58 (m, 3H), 1.25 (m, 3H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.3.

#### Example M40

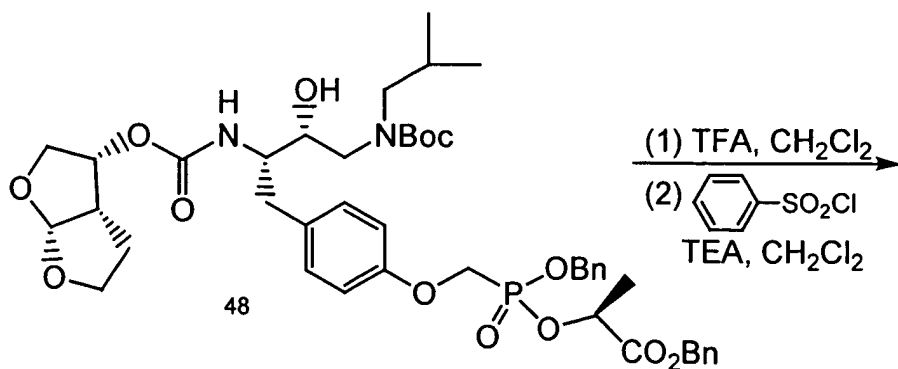
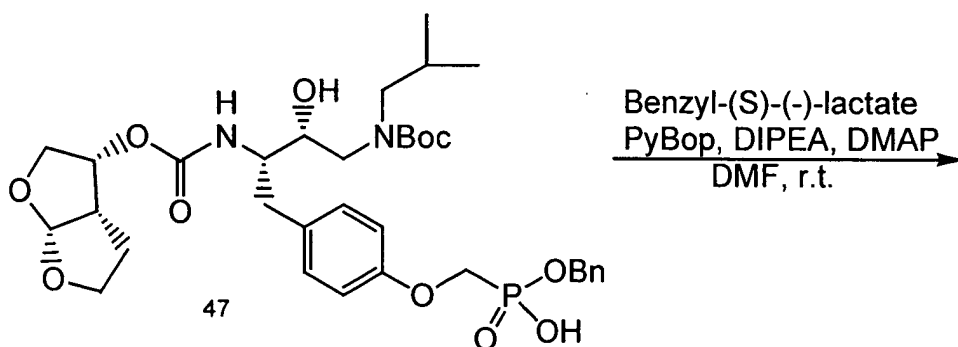
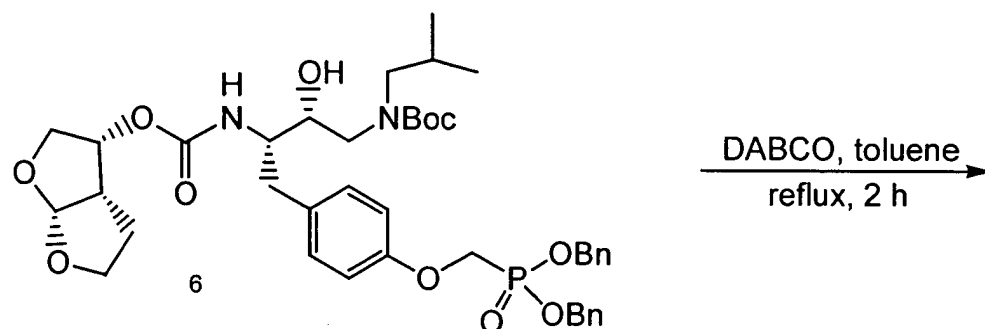
Monophospholactate 45: A solution of 43 (0.12 g, 0.16 mmol) and lactate 44 (0.22 g, 1.02 mmol) in pyridine (1 mL) was heated to  $70^\circ\text{C}$  and 1,3-dicyclohexylcarbodiimide (0.17 g, 0.83 mmol) was added. The reaction mixture was stirred at  $70^\circ\text{C}$  for 4 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl,  $\text{H}_2\text{O}$ , saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (45 mg, 26%) as a white solid.

#### Example M41

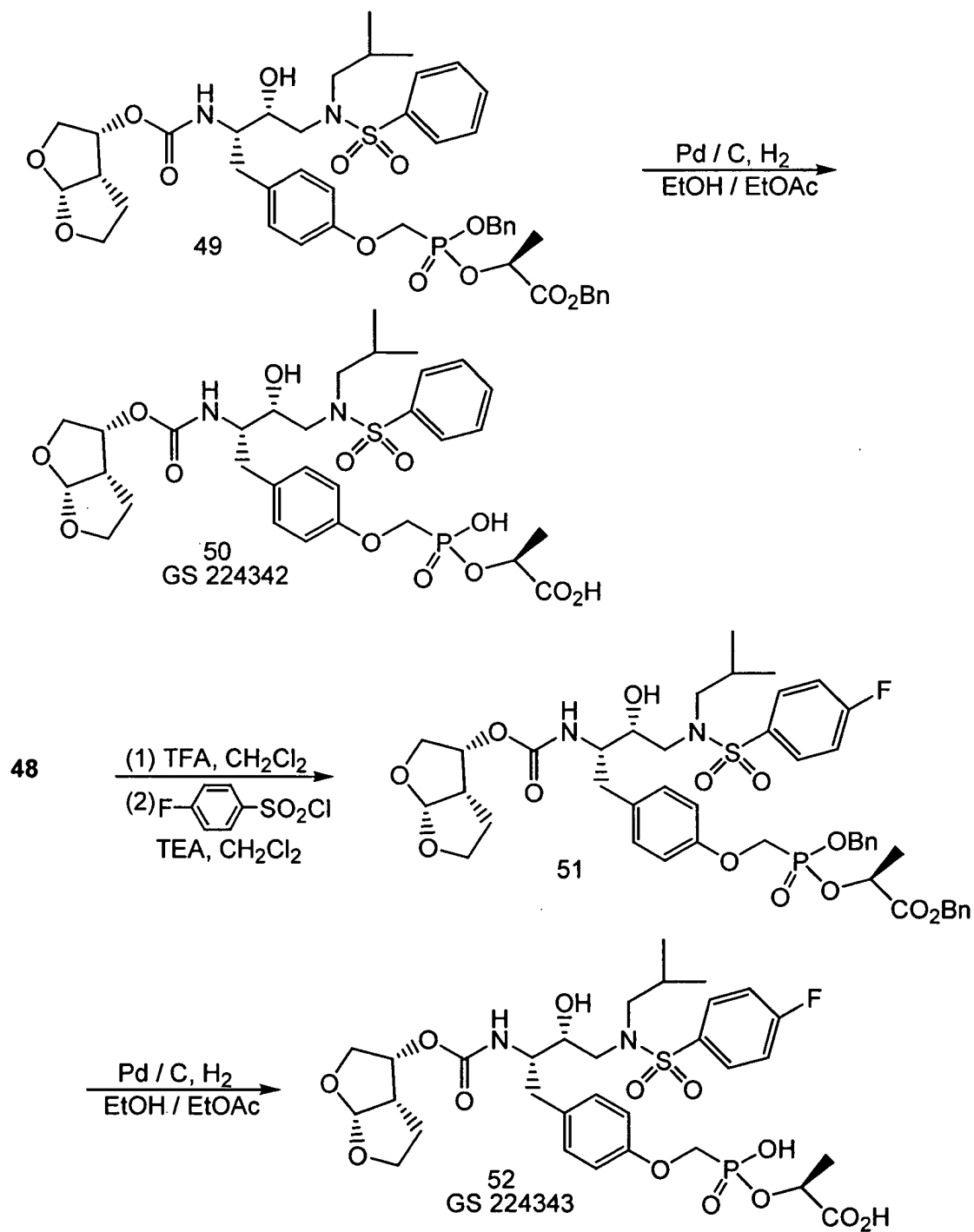
Alcohol 46: To a solution of 45 (40 mg, 0.042 mmol) in EtOAc (2 mL) was added 20%  $\text{Pd}(\text{OH})_2/\text{C}$  (10 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the product was dried under vacuum to give the alcohol (33 mg, 90%, GS

278809, 3/2 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.7 Hz, 2H), 7.39-7.15 (m, 7H), 7.02-6.88 (m, 4H), 5.66 (d,  $J$  = 4.5 Hz, 1H), 5.13-5.02 (m, 2H), 4.54-4.10 (m, 4H), 4.00-3.69 (m, 11H), 3.14 (m, 1H), 3.02-2.77 (m, 6H), 1.85-1.6 (m, 6H), 0.94 (d,  $J$  = 6.3 Hz, 3H), 0.89 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4, 15.9.

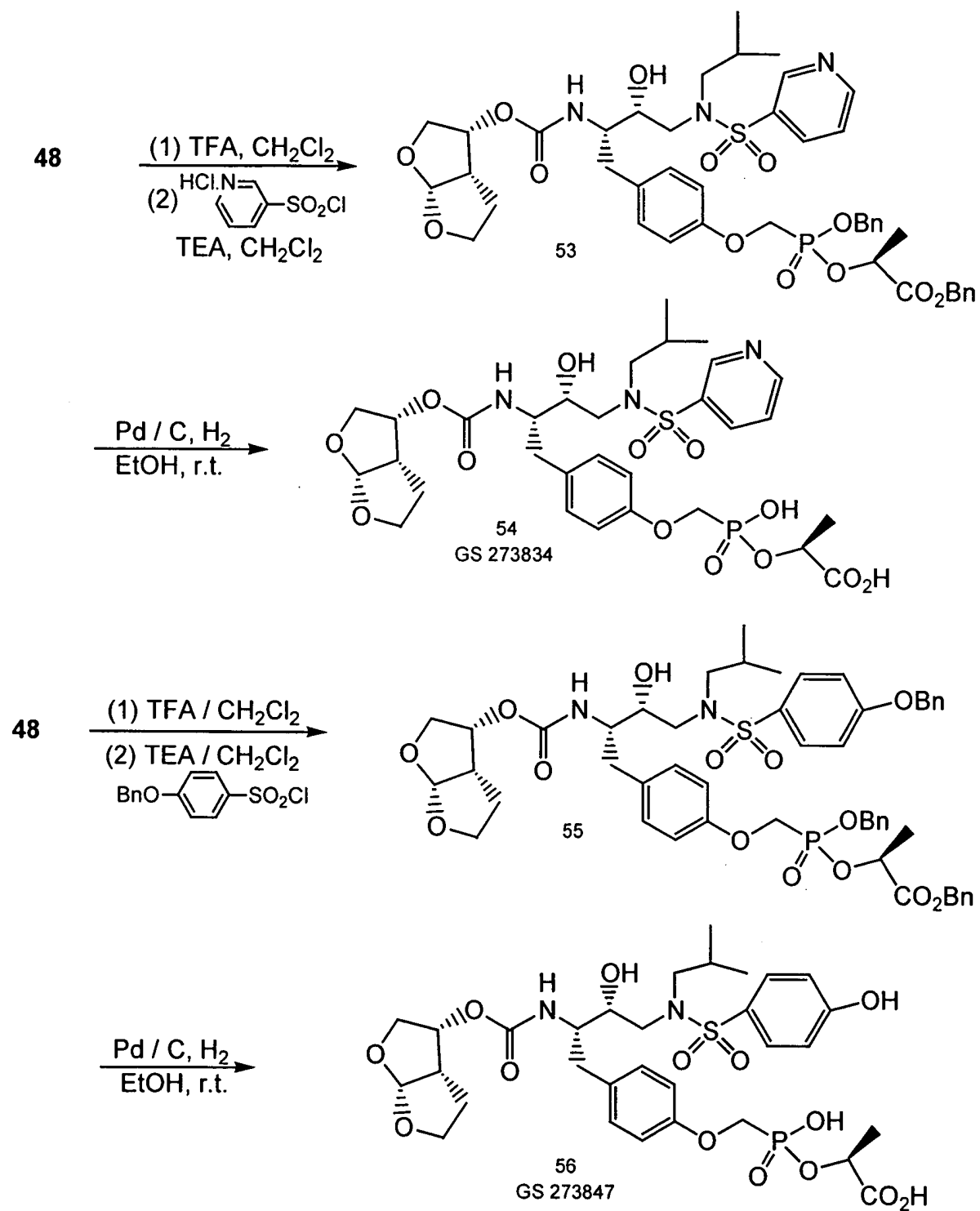
# **Scheme M12**



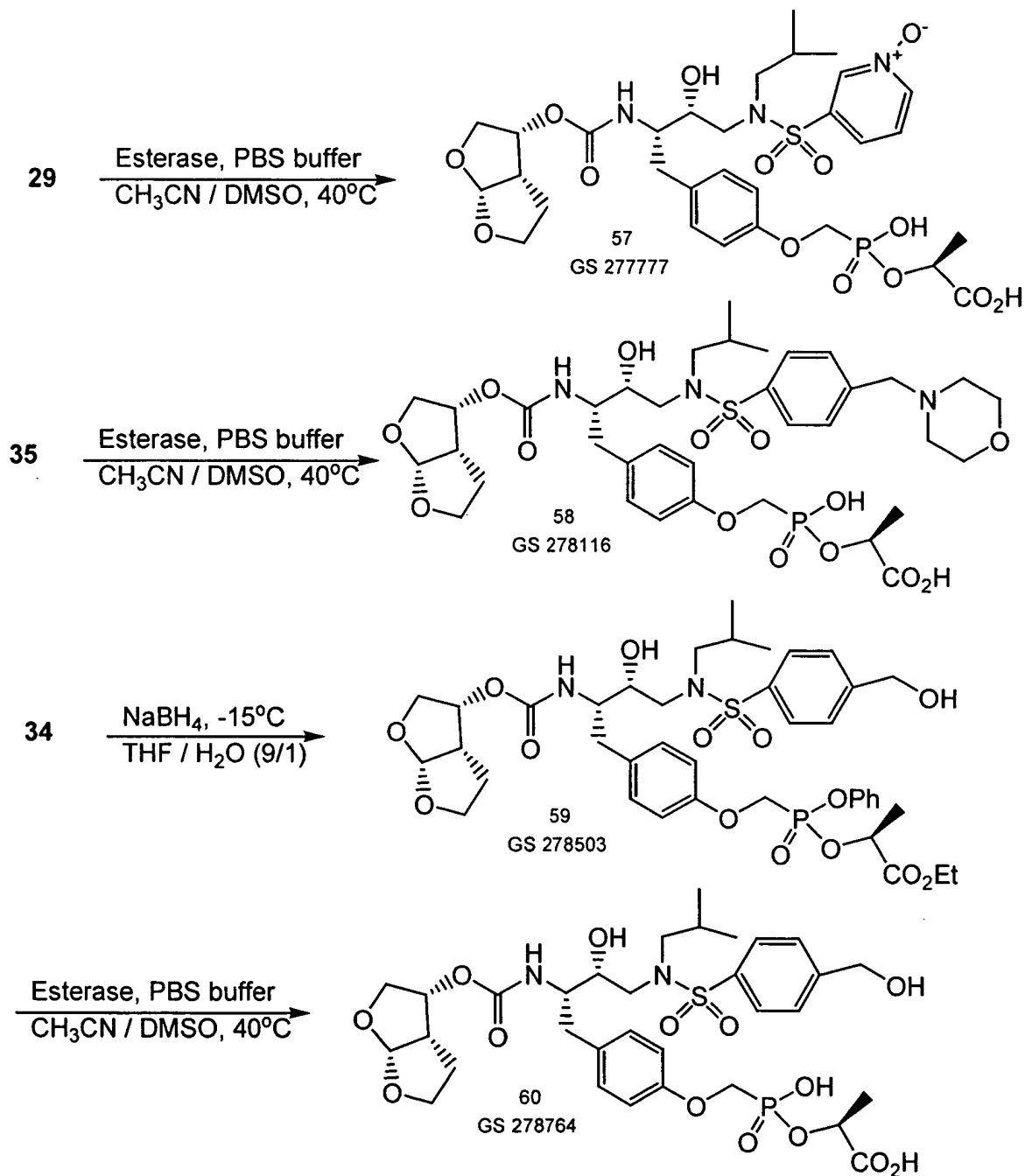
**Scheme M13**



Scheme M14



## Scheme M15



## Example M42

**Monobenzylphosphonate 47:** A solution of **6** (2.00 g, 2.55 mmol) and DABCO (0.29 g, 2.55 mmol) in toluene (10 mL) was heated to reflux for 2 h. The solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer

was washed with H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was dried under vacuum to give the monobenzylphosphonate (1.68 g, 95%) as a white solid.

#### Example M43

Monophospholactate 48: To a solution of 47 (2.5 g, 3.61 mmol) and benzyl-(S)-(-)-lactate (0.87 mL, 5.42 mmol) in DMF (12 mL) was added PyBop (2.82 g, 5.42 mmol) and *N,N*-diisopropylethylamine (2.51 mL, 14.44 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (1.58 g, 51%) as a white solid.

#### Example M44

Monophospholactate 49: A solution of 48 (0.30 g, 0.35 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) at 0°C was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and cooled to 0°C. Triethylamine (0.20 mL, 1.40 mmol) was added followed by the treatment of benzenesulfonyl chloride (62 mg, 0.35 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.17 g, 53%) as a white solid.

#### Example M45

Metabolite X 50: To a solution of 49 (80 mg, 0.09 mmol) in EtOH (6 mL) and EtOAc (2 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 8 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with CHCl<sub>3</sub> and dried under vacuum to give the

metabolite X (61 mg, 95%, GS 224342) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.83 (d,  $J$  = 6.9 Hz, 2H), 7.65-7.58 (m, 3H), 7.18 (d,  $J$  = 7.8 Hz, 2H), 6.90 (d,  $J$  = 7.8 Hz, 2H), 5.59 (d,  $J$  = 4.8 Hz, 1H), 5.0 (m, 1H), 4.27 (d,  $J$  = 10.2 Hz, 2H), 3.95-3.68 (m, 6H), 3.45 (dd, 1H), 3.18-2.84 (m, 6H), 2.50 (m, 1H), 2.02 (m, 1H), 1.6-1.38 (m, 5H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ ),  $\delta$  18.0.

#### Example M46

Monophospholactate 51: A solution of 48 (0.28 g, 0.33 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.6 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.18 mL, 1.32 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (64 mg, 0.33 mmol). The solution was stirred at  $0^\circ\text{C}$  for 30 min and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.16 g, 52%) as a white solid.

#### Example M47

Metabolite X 52: To a solution of 51 (80 mg, 0.09 mmol) in EtOH (6 mL) and EtOAc (2 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 8 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with  $\text{CHCl}_3$  and dried under vacuum to give the metabolite X (61 mg, 95%, GS 224343) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.9 (dd, 2H), 7.32 (m, 2H), 7.18 (dd, 2H), 6.90 (dd, 2H), 5.59 (d,  $J$  = 5.4 Hz, 1H), 5.0 (m, 1H), 4.28 (d,  $J$  = 10.2 Hz, 2H), 3.95-3.72 (m, 6H), 3.44 (dd, 1H), 3.15-2.85 (m, 6H), 2.5 (m, 1H), 2.02 (m, 1H), 1.55-1.38 (m, 5H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H).  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  18.2.

#### Example M48

Monophospholactate 53: A solution of 48 (0.20 g, 0.24 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.6 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.16 mL, 1.20 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinysulfonyl chloride (50 mg, 0.24 mmol). The solution was stirred at  $0^\circ\text{C}$  for 30 min and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.11 g, 53%) as a white solid.

#### Example M49

Metabolite X 54: To a solution of 53 (70 mg, 0.09 mmol) in EtOH (5 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 5 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with  $\text{CHCl}_3$  and dried under vacuum to give the metabolite X (53 mg, 95%, GS 273834) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.99 (s, 1H), 8.79 (d,  $J$  = 4.2 Hz, 1H), 8.29 (d,  $J$  = 7.5 Hz, 1H), 7.7 (m, 1H), 7.15 (d,  $J$  = 8.4 Hz, 2H), 6.9 (d,  $J$  = 7.8 Hz, 2H), 5.59 (d,  $J$  = 5.4 Hz, 1H), 5.0 (m, 1H), 4.28 (d,  $J$  = 9.9 Hz, 2H), 3.97-3.70 (m, 6H), 3.44 (dd, 1H), 3.17-2.85 (m, 6H), 2.5 (m, 1H), 2.03 (m, 1H), 1.65-1.38 (m, 5H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H).  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  17.8.

#### Example M50

Monophospholactate 55: A solution of 48 (0.15 g, 0.18 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.12 mL, 0.88 mmol) was

added followed by the treatment of 4-benzyloxybenzenesulfonyl chloride (50 mg, 0.18 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.11 g, 63%) as a white solid.

#### Example M51

Metabolite X 56: To a solution of 55 (70 mg, 0.07 mmol) in EtOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with CHCl<sub>3</sub> and dried under vacuum to give the metabolite X (46 mg, 90%, GS 273847) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD), δ 7.91 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.91 (m, 4H), 5.59 (d, J = 5.1 Hz, 1H), 5.0 (m, 1H), 4.27 (d, J = 10.2 Hz, 2H), 3.97-3.74 (m, 6H), 3.4 (dd, 1H), 3.17-2.8 (m, 6H), 2.5 (m, 1H), 2.0 (m, 1H), 1.6-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 17.9.

#### Example M52

Metabolite X 57: To a suspension of 29 (40 mg, 0.05 mmol) in CH<sub>3</sub>CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (200 μL). The suspension was heated to 40°C for 48 h. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (20 mg, 57%, GS 277777) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.68 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.68 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.4 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.0 (m, 1H), 4.23 (d, J = 10.5 Hz, 2H), 3.97-3.68 (m, 6H), 3.45 (dd, 1H), 3.15-2.87 (m, 6H), 2.46 (m, 1H), 2.0 (m, 1H), 1.6-1.38 (m, 5H), 0.95 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 17.2.

#### Example M53

Metabolite X 58: To a suspension of 35 (60 mg, 0.07 mmol) in CH<sub>3</sub>CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (400 μL). The suspension was heated to 40°C for 3 days. The reaction mixture was concentrated, suspended in MeOH and

filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (20 mg, 38%, GS 278116) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.74 (d,  $J$  = 6.9 Hz, 2H), 7.63 (d,  $J$  = 7.5 Hz, 2H), 7.21 (d,  $J$  = 8.4 Hz, 2H), 6.95 (d,  $J$  = 8.1 Hz, 2H), 5.64 (d,  $J$  = 5.1 Hz, 1H), 5.0 (m, 2H), 4.41 (m, 2H), 4.22 (m, 2H), 3.97-3.65 (m, 12H), 3.15-2.9 (m, 8H), 2.75 (m, 1H), 2.0 (m, 1H), 1.8 (m, 2H), 1.53 (d,  $J$  = 6.9 Hz, 3H), 0.88 (m, 6H).

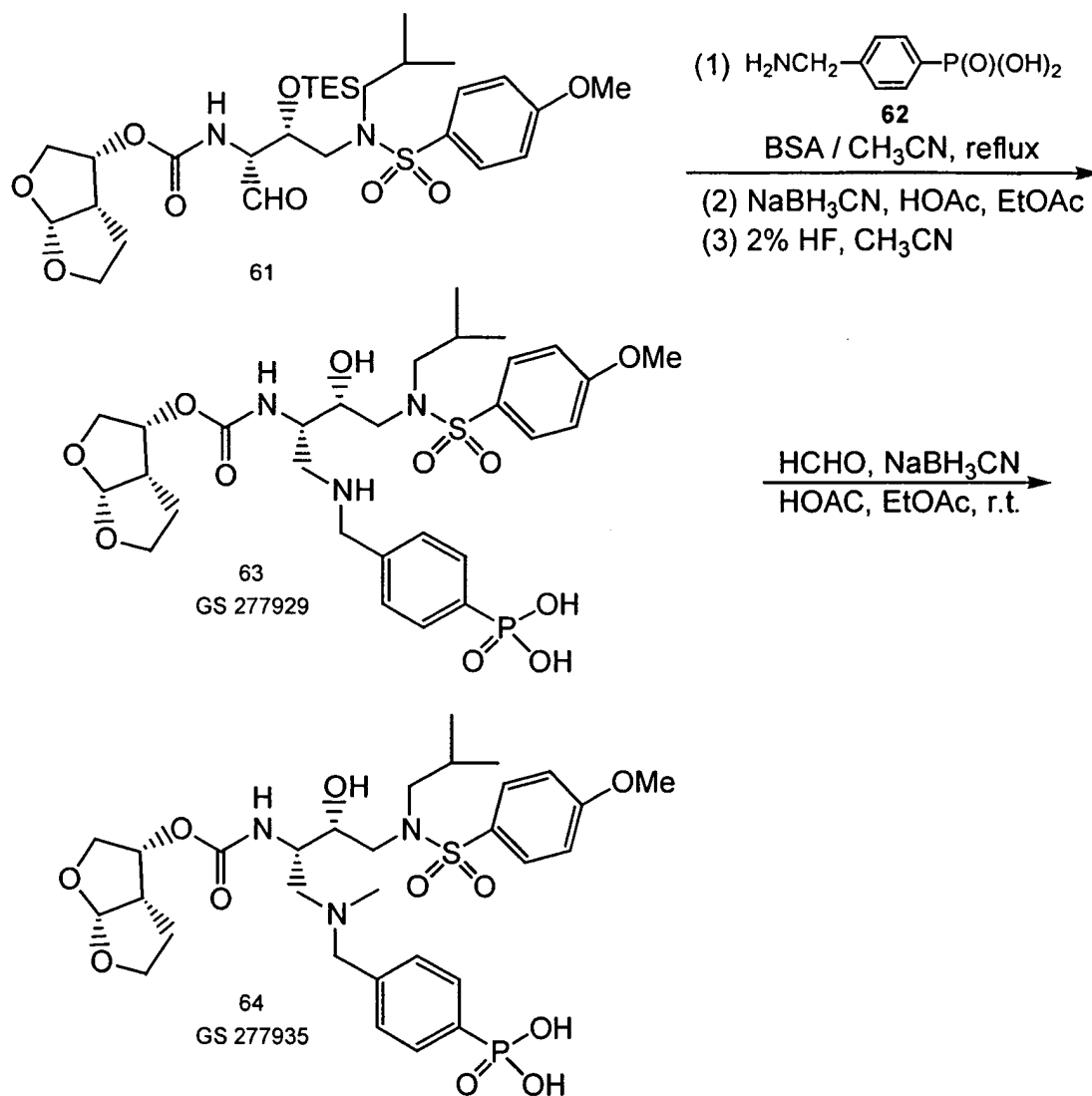
#### Example M54

Monophospholactate 59: A solution of 34 (2.10 g, 2.48 mmol) in THF (72 mL) and  $\text{H}_2\text{O}$  (8 mL) at  $-15^\circ\text{C}$  was treated with  $\text{NaBH}_4$  (0.24 g, 6.20 mmol). The reaction mixture was stirred for 10 min at  $-15^\circ\text{C}$ . The reaction was quenched with 5% aqueous  $\text{NaHSO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x). The combined organic layers were washed with  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (5% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give monophospholactate (1.89 g, 90%, GS 278053, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.64 (m, 2H), 7.51 (m, 2H), 7.38-7.19 (m, 7H), 6.92 (m, 2H), 5.69 (d,  $J$  = 4.8 Hz, 1H), 5.15 (m, 2H), 4.76 (s, 2H), 4.54 (d,  $J$  = 10.5 Hz, 1H), 4.44 (m, 1H), 4.2 (m, 2H), 4.04-3.68 (m, 6H), 3.06-2.62 (m, 7H), 1.8 (m, 3H), 1.62-1.5 (dd, 3H), 1.25 (m, 3H), 0.94 (d,  $J$  = 6.3 Hz, 3H), 0.87 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4, 15.4.

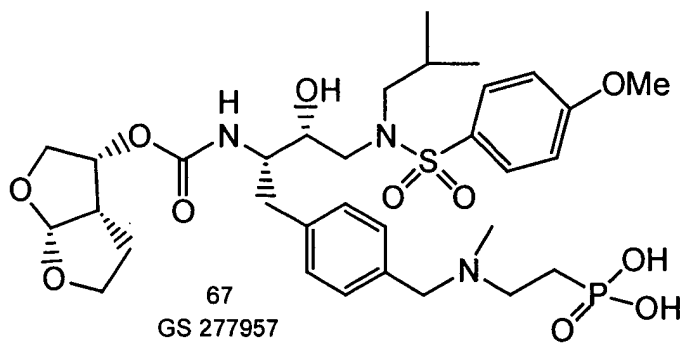
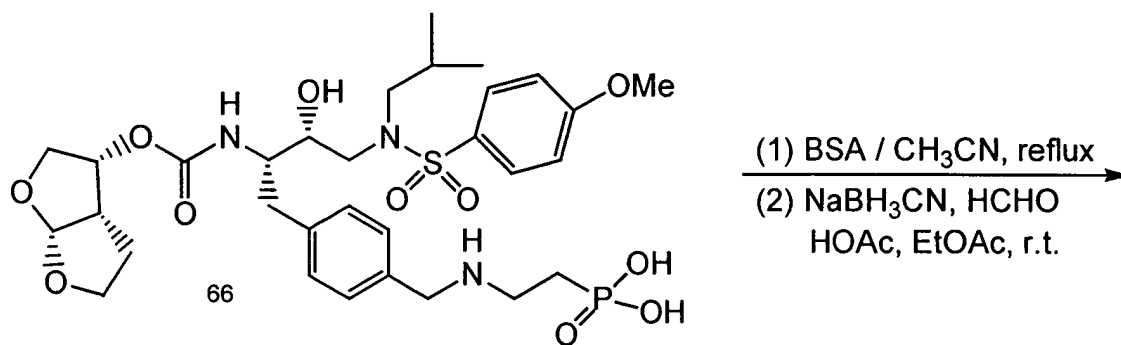
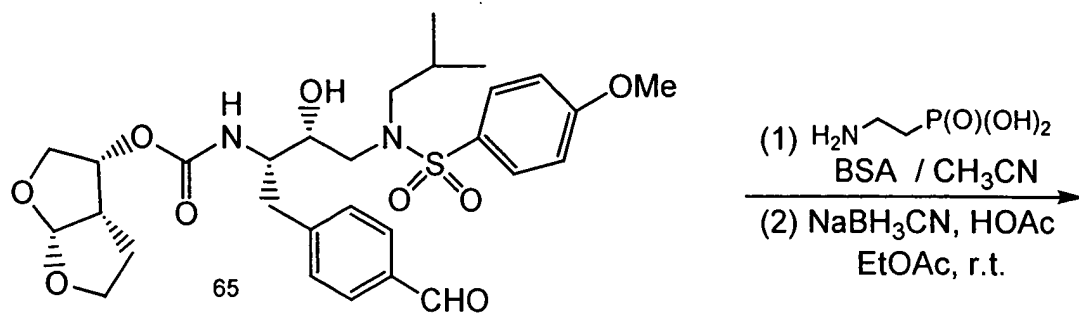
#### Example M55

Metabolite X 60: To a suspension of 59 (70 mg, 0.08 mmol) in  $\text{CH}_3\text{CN}$  (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (600  $\mu\text{L}$ ). The suspension was heated to  $40^\circ\text{C}$  for 36 h. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (22 mg, 36%, GS 278764) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.78 (dd, 2H), 7.54 (dd, 2H), 7.15 (m, 2H), 6.9 (m, 2H), 5.57 (d, 1H), 5.0 (m, 2H), 4.65 (m, 4H), 4.2 (m, 2H), 3.9-3.53 (m, 6H), 3.06-2.82 (m, 6H), 2.5 (m, 1H), 2.0 (m, 2H), 1.62-1.35 (m, 3H), 0.94 (m, 6H).

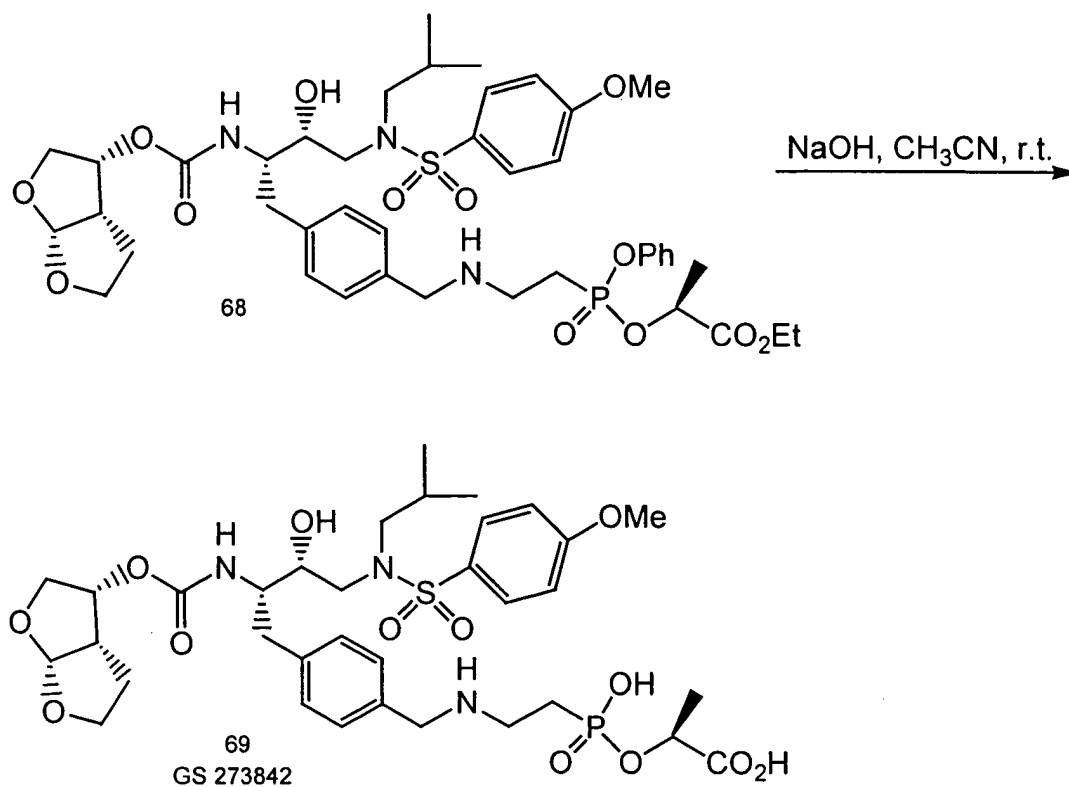
Scheme M16



**Scheme M17**



## Scheme M18



## Example M56

Phosphonic Acid 63: Compound 62 (0.30 g, 1.12 mmol) was dissolved in CH<sub>3</sub>CN (5 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 2.2 mL, 8.96 mmol) was added. The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (4 mL) and cooled to 0°C. Aldehyde 61 (0.20 g, 0.33 mmol), AcOH (0.18 mL, 3.30 mmol), and NaBH<sub>3</sub>CN (0.20 g, 3.30 mmol) were added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with H<sub>2</sub>O, stirred for 30 min, filtered, and concentrated. The crude product was dissolved in CH<sub>3</sub>CN (13 mL) and 48% aqueous HF (0.5 mL) was added. The reaction mixture was stirred at room temperature for 2 h and concentrated. The crude product was purified by HPLC to give the phosphonic acid (70 mg, 32%, GS 277929) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.92 (dd, 2H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.63 (dd, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 5.68 (d, *J* = 5.1 Hz, 1H), 5.13 (m, 1H), 4.4 (m, 2H), 4.05-3.89 (m, 8H), 3.75 (m, 1H), 3.5 (m, 1H), 3.37 (m, 1H), 3.23-3.0 (m,

3H), 2.88-2.7 (m, 2H), 2.2 (m, 1H), 1.8 (m, 2H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.85 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  14.5.

#### Example M57

Phosphonic Acid 64: A solution of 63 (50 mg, 0.07 mmol) and formaldehyde (60 mg, 0.70 mmol) in EtOAc (2 mL) was treated with HOAc (43  $\mu\text{L}$ , 0.70 mmol) and  $\text{NaBH}_3\text{CN}$  (47 mg, 0.7 mmol). The reaction mixture was stirred at room temperature for 26 h. The reaction was quenched with  $\text{H}_2\text{O}$ , stirred for 20 min, and concentrated. The crude product was purified by HPLC to give the phosphonic acid (15 mg, 29%, **GS 277935**) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.93 (m, 2H), 7.75 (m, 2H), 7.62 (m, 2H), 7.11 (m, 2H), 5.66 (m, 1H), 5.13 (m, 1H), 4.4 (m, 2H), 4.05-3.89 (m, 8H), 3.75 (m, 2H), 3.09-2.71 (m, 6H), 2.2 (m, 1H), 1.9 (m, 5H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.85 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  14.0.

#### Example M58

Phosphonic Acid 66: 2-Aminoethylphosphonic acid (2.60 g, 21.66 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (40 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 40 mL) was added. The reaction mixture was heated to reflux for 2 h and cooled to room temperature and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (40 mL). Aldehyde 65 (1.33 g, 2.25 mmol), AcOH (1.30 mL, 22.5 mmol) and  $\text{NaBH}_3\text{CN}$  (1.42 g, 22.5 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with  $\text{H}_2\text{O}$ , stirred for 1 h, filtered, and concentrated. The residue was dissolved in MeOH and filtered. The crude product was purified by HPLC to give the phosphonic acid (1.00 g, 63%) as a white solid.

#### Example M59

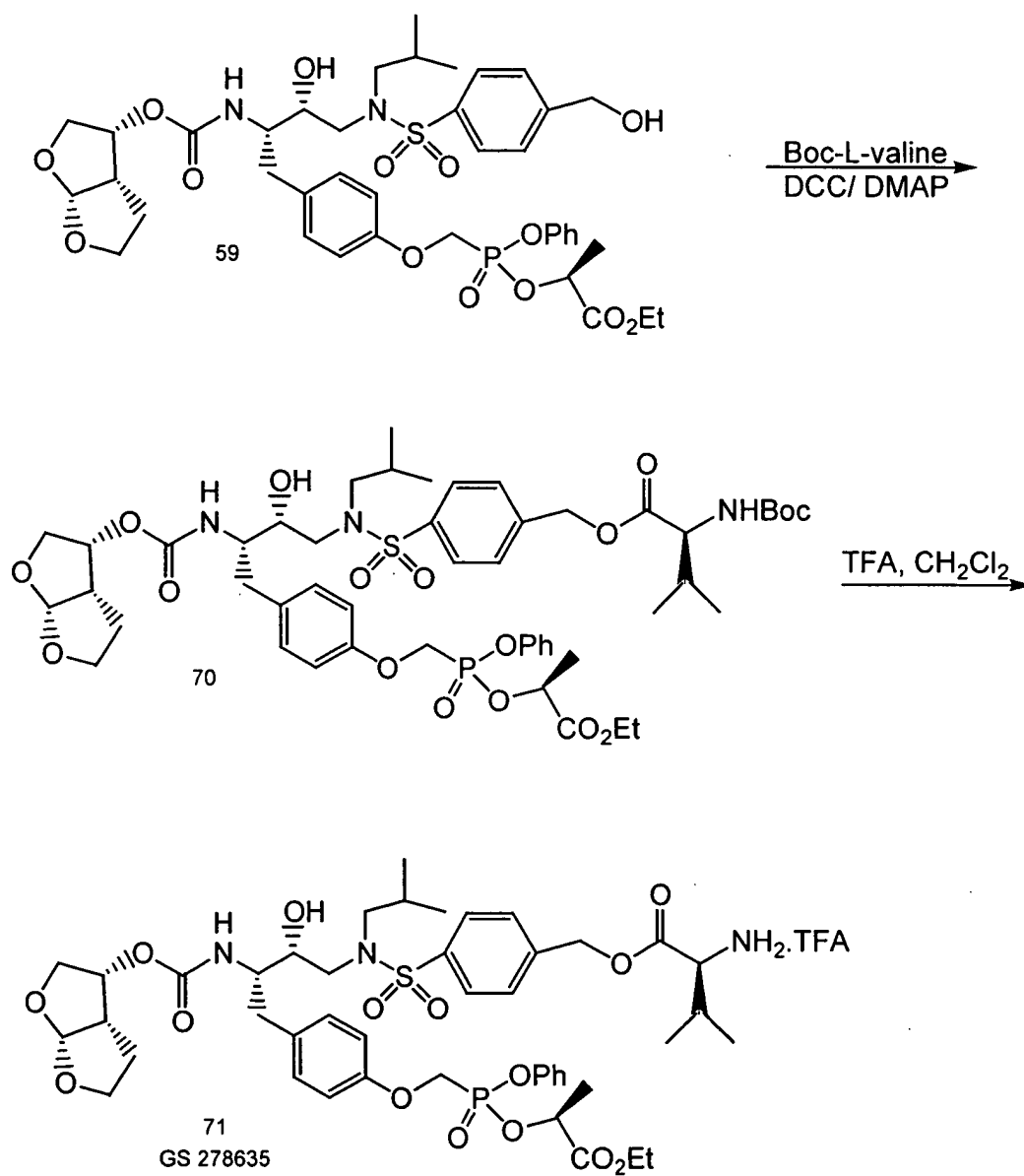
Phosphonic Acid 67: Phosphonic acid 66 (0.13 g, 0.19 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (4 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.45 mL, 1.90 mmol) was added. The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (3 mL). Formaldehyde (0.15 mL, 1.90 mmol), AcOH (0.11 mL, 1.90 mmol) and  $\text{NaBH}_3\text{CN}$  (63 mg, 1.90 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with  $\text{H}_2\text{O}$ , stirred for 6 h, filtered, and

concentrated. The residue was dissolved in MeOH and filtered. The crude product was purified by HPLC to give the phosphonic acid (40 mg, 30%, GS 277957) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.78 (d,  $J$  = 8.4 Hz, 2H), 7.4 (m, 4H), 7.09 (d,  $J$  = 8.4 Hz, 2H), 5.6 (d,  $J$  = 5.1 Hz, 1H), 4.33 (m, 2H), 3.95-3.65 (m, 9H), 3.5-3.05 (m, 6H), 2.91-2.6 (m, 7H), 2.0 (m, 3H), 1.5 (m, 2H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.87 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  19.7.

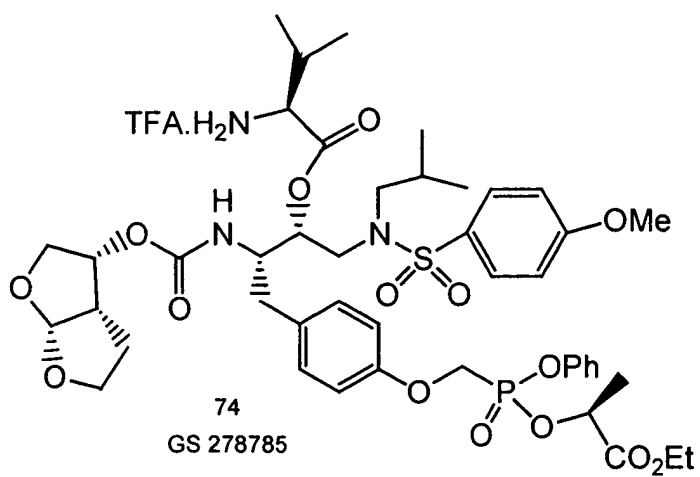
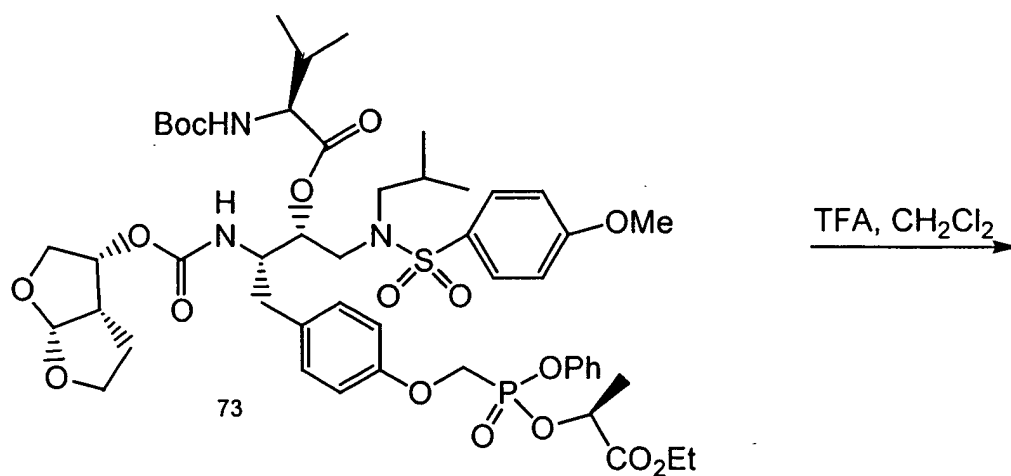
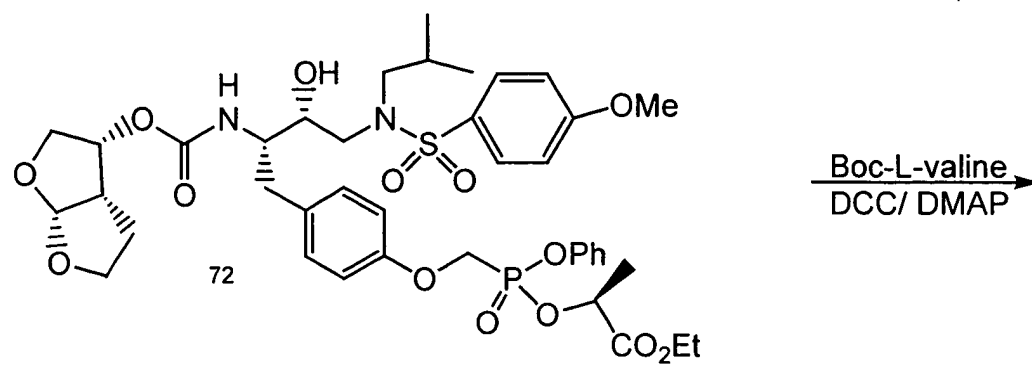
#### Example M60

Metabolite X 69: Monophospholactate 68 (1.4 g, 1.60 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (20 mL) and  $\text{H}_2\text{O}$  (20 mL). 1.0 N NaOH (3.20 mL, 3.20 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h and cooled to  $0^\circ\text{C}$ . The reaction mixture was acidified to pH = 1-2 with 2 N HCl (1.6 mL, 3.20 mmol). The solvent was evaporated under reduced pressure. The crude product was purified by HPLC to give the metabolite X (0.60 g, 49%, GS 273842) as a white solid:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.72 (d,  $J$  = 8.7 Hz, 2H), 7.33 (m, 4H), 7.09 (d,  $J$  = 9.0 Hz, 2H), 5.52 (d,  $J$  = 5.7 Hz, 1H), 5.1 (broad, s, 1H), 4.85 (m, 1H), 4.63 (m, 1H), 4.13 (m, 2H), 3.8 (m, 5H), 3.6 (m, 4H), 3.36 (m, 1H), 3.03 (m, 4H), 2.79 (m, 3H), 2.5 (m, 1H), 2.0 (m, 3H), 1.5-1.3 (m, 5H), 0.85 (d,  $J$  = 6.6 Hz, 3H), 0.79 (d,  $J$  = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  21.9.

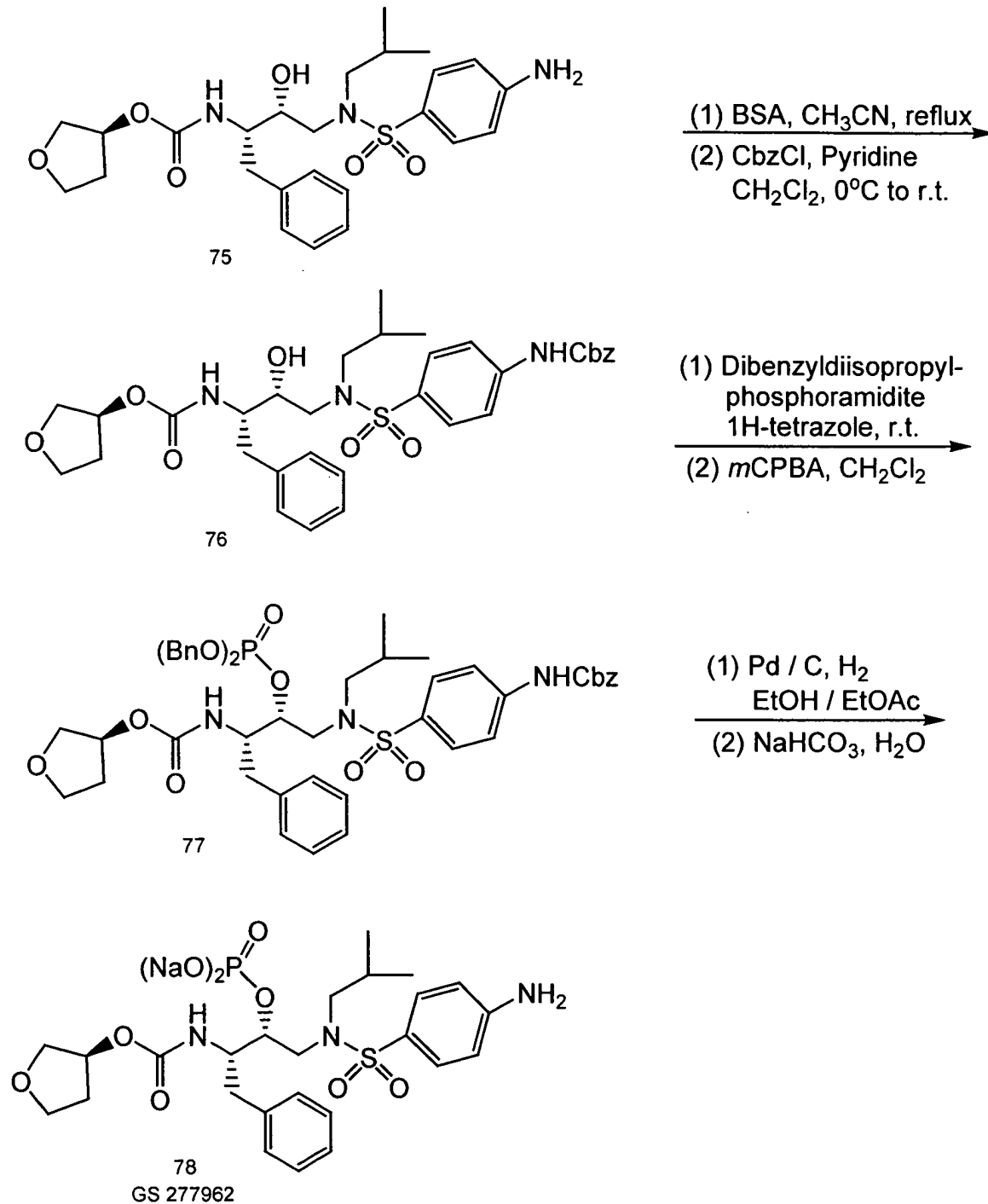
**Scheme M19**



**Scheme M20**



## Scheme M21



## Example M61

Monophospholactate 70: A solution of 59 (1.48 g, 1.74 mmol) and Boc-L-valine (0.38 g, 1.74 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0°C was treated with 1,3- dicyclohexylcarbodiimide (0.45 g,

2.18 mmol) and 4-dimethylaminopyridine (26 mg, 0.21 mmol). The reaction mixture was stirred at 0°C for 1 h and then warmed to room temperature for 2 h. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 0.2 N HCl. The organic layer was washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (1.65 g, 90%) as a white solid.

#### Example M62

Monophospholactate 71: A solution of 70 (1.65 g, 1.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) at 0°C was treated with trifluoroacetic acid (4 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (1.42 g, 85%, GS 278635, 2/3 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (m, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.4-7.1 (m, 7H), 6.89 (m, 2H), 5.64 (m, 1H), 5.47 (m, 1H), 5.33-5.06 (m, 4H), 4.57-4.41 (m, 2H), 4.2 (m, 2H), 3.96-3.7 (m, 7H), 3.15-2.73 (m, 7H), 2.38 (m, 1H), 1.9 (m, 1H), 1.7 (m, 1H), 1.63-1.5 (m, 4H), 1.24 (m, 3H), 1.19 (m, 6H), 0.91 (d, 3H), 0.88 (d, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.3, 15.4.

#### Example M63

Monophospholactate 73: A solution of 72 (0.43 g, 0.50 mmol) and Boc-L-valine (0.11 g, 0.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) was treated with 1,3-dicyclohexylcarbodiimide (0.13 g, 0.63 mmol) and 4-dimethylaminopyridine (62 mg, 0.5 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 0.2 N HCl. The organic layer was washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.45 g, 85%) as a white solid.

#### Example M64

Monophospholactate 74: A solution of 73 (0.44 g, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at 0°C was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The crude product was purified by

column chromatography on silica gel (10% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.40 g, 90%, GS 278785, 1:1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.69 (d, J = 8.4 Hz, 2H), 7.34-7.2 (m, 7H), 6.98 (d, J = 8.4 Hz, 2H), 6.88 (m, 2H), 6.16 (m, 1H), 5.64 (m, 1H), 5.46 (m, 1H), 5.2-5.0 (m, 2H), 4.5 (m, 2H), 4.2 (m, 3H), 4.0-3.4 (m, 9H), 3.3 (m, 1H), 3.0-2.8 (m, 5H), 2.5 (m, 1H), 1.83 (m, 1H), 1.6-1.5 (m, 5H), 125 (m, 3H), 1.15 (m, 6H), 0.82 (d, J = 6.0 Hz, 3H), 0.76 (d, J = 6.0 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.3, 15.5.

#### Example M65

**Cbz Amide 76:** Compound 75 (0.35 g, 0.69 mmol) was dissolved in CH<sub>3</sub>CN (6 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.67 mL, 2.76 mmol) was added. The reaction mixture was heated to reflux for 1 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and cooled to 0°C. Pyridine (0.17 mL, 2.07 mmol) and benzyl chloroformate (0.12 mL, 0.83 mmol) were added. The reaction mixture was stirred at 0°C for 1 h and then warmed to room temperature overnight. The reaction was quenched with MeOH (5 mL) and 10% HCl (20 mL) at 0°C and stirred for 1 h. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the CBz amide (0.40 g, 90%) as a white solid.

#### Example M66

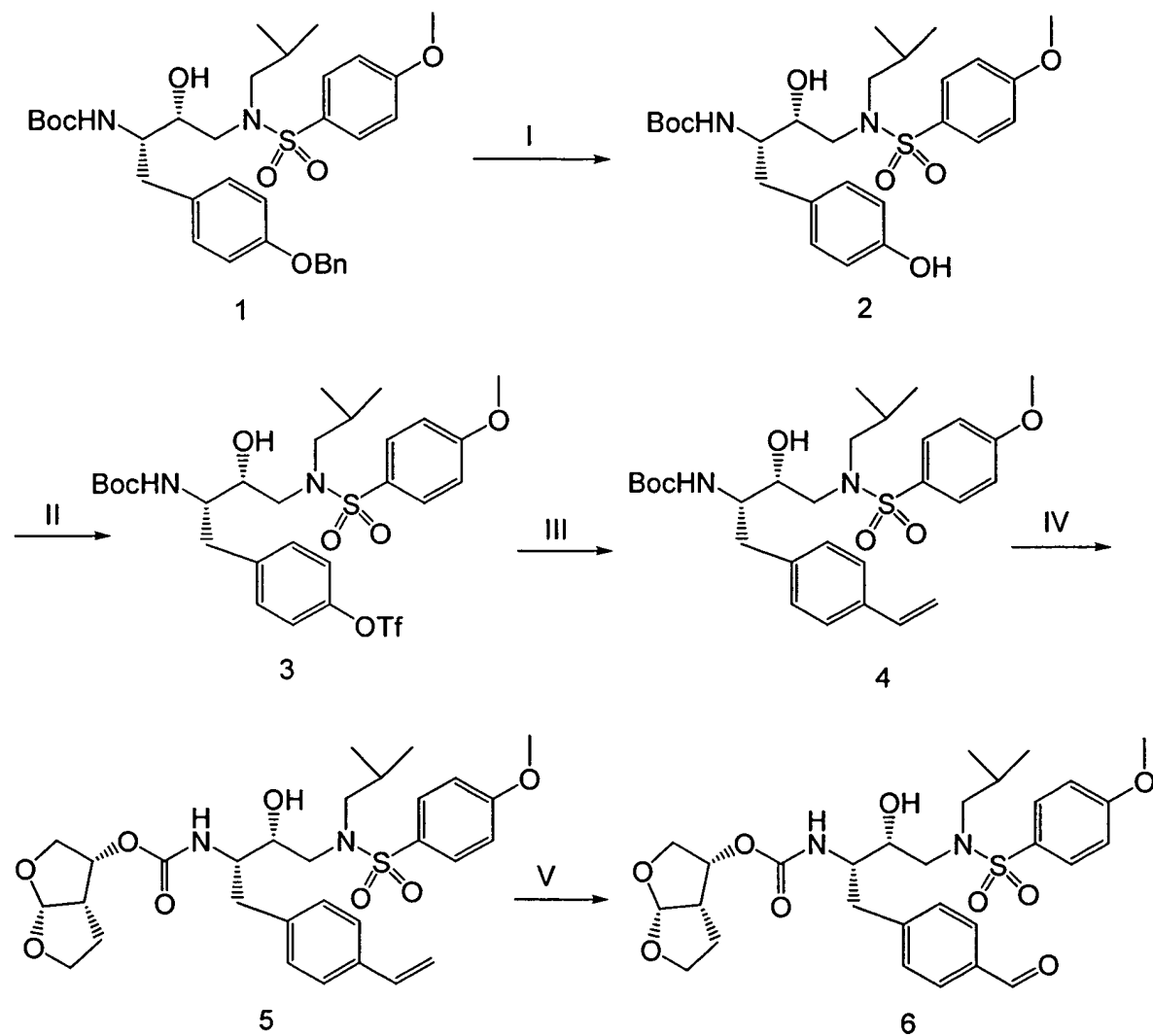
**Dibenzylphosphonate 77:** A solution of 76 (0.39 g, 0.61 mmol) and 1*H*-tetrazole (54 mg, 0.92 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was treated with dibenzyl-diisopropylphosphoramidite (0.32 g, 0.92 mmol) and stirred at room temperature overnight. The solution was cooled to 0°C, treated with *m*CPBA, stirred for 1 h at 0°C and then warmed to room temperature for 1 h. The reaction mixture was poured into a mixture of aqueous Na<sub>2</sub>SO<sub>3</sub> and NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the dibenzylphosphonate (0.42 g, 76%) as a white solid.

### Example M67

Disodium Salt of Phosphonic Acid 78: To a solution of 77 (0.18 g, 0.20 mmol) in EtOH (20 mL) and EtOAc (4 mL) was added 10% Pd/C (40 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (0.11 g, 95%) which was dissolved in H<sub>2</sub>O (4 mL) and treated with NaHCO<sub>3</sub> (32 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (0.12 g, 99%, GS 277962) as a white solid: <sup>1</sup>H NMR (D<sub>2</sub>O) δ 7.55 (dd, 2H), 7.2 (m, 5H), 7.77 (dd, 2H), 4.65 (m, 1H), 4.24 (m, 1H), 4.07 (m, 1H), 3.78-2.6 (m, 12H), 1.88-1.6 (m, 3H), 0.75 (m, 6H).

## Example Section N

Scheme N1



I.  $\text{H}_2/10\%\text{Pd-C}/\text{EtOAc-EtOH}$  ; II.  $\text{Tf}_2\text{NPh}/\text{Cs}_2\text{CO}_3$ ;  
III.  $\text{Bu}_3\text{SnCH=CH}_2/\text{PdCl}_2(\text{PPh}_3)_2/\text{LiCl}/\text{DMF}/90\text{ }^\circ\text{C}$ ;  
IV. a.  $\text{TFA}/\text{CH}_2\text{Cl}_2$ ; b. Bisfurancarboxylate/ $i\text{-Pr}_2\text{NEt}/\text{DMAP}$ ;  
V.  $\text{NaIO}_4/\text{OsO}_4/\text{EtOAc-H}_2\text{O}$

## Example N1

Compound 1 was prepared by methods from Examples herein.

#### Example N2

Compound 2: To a solution of compound 1 (47.3 g) in EtOH/EtOAc (1000 mL/500 mL) was added 10% Pd-C (5 g). The mixture was hydrogenated for 19 hours. Celite was added and the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and was washed with ethyl acetate. Concentration gave compound 2 (42.1 g).

#### Example N3

Compound 3: To a solution of compound 2 (42.3 g, 81 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (833 mL) was added N-phenyltrifluoromethanesulfonimide (31.8 g, 89 mmol), followed by cesium carbonate (28.9 g, 89 mmol). The mixture was stirred for 24 hours. The solvent was removed under reduced pressure, and ethyl acetate was added. The reaction mixture was washed with water (3x) and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc = 13/1) gave compound 3 (49.5 g) as a white powder.

#### Example N4

Compound 4: To a solution of compound 3 (25.2, 38.5 mmol) in DMF (240 mL) was added lithium chloride (11.45 g, 270 mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (540 mg, 0.77 mmol). The mixture was stirred for 3 minutes under high vacuum and recharged with nitrogen. To the above solution was added tributylvinyltin (11.25 mL). The reaction mixture was heated at 90°C for 6 hours and cooled to 25°C. Water was added to the reaction, and the mixture was extracted with ethyl acetate (3X). The combined organic layer was washed with water (6x) and brine, and dried over MgSO<sub>4</sub>. Concentration gave an oil. The oil was diluted with dichloromethane (40 mL), water (0.693 mL, 38.5 mmol) and DBU (5.76 mL, 38.5 mmol) were added. The mixture was stirred for 5 minutes, and subjected to flash column chromatography (hexanes/EtOAc = 2.5/1). Compound 4 was obtained as white solid (18.4 g).

#### Example N5

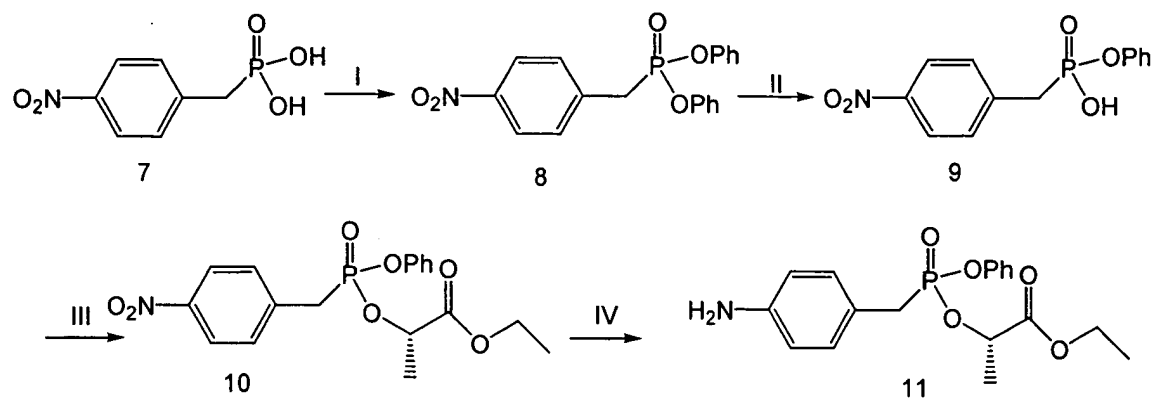
Compound 5: To a solution of compound 4 (18.4 g, 34.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (70 mL) at 0°C was added trifluoroacetic acid (35 mL). The mixture was stirred at 0°C for 2 hrs, and solvents were evaporated under reduced pressure. The reaction mixture was quenched with saturated sodium carbonate solution, and was extracted with ethyl acetate (3x). The combined organic layer was washed with saturated sodium carbonate solution(1x), water (2x), and brine

(1x), and dried over  $\text{MgSO}_4$ . Concentration gave a solid. To a solution of the above solid in acetonitrile (220 mL) at  $0^\circ\text{C}$  was added bisfurancarboxylate (10.09 g, 34.2 mmol), followed by diisopropylethylamine (12.0 mL, 69.1 mmol) and DMAP (843 mg, 6.9 mmol). The mixture was warmed to  $25^\circ\text{C}$  and stirred for 12 hours. Solvents were removed under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2X), 5% hydrochloric acid (2x), water (2x), 1N sodium hydroxide (2x), water (2x), and brine (1x), and dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 1/1) gave compound 5 (13.5 g).

#### Example N6

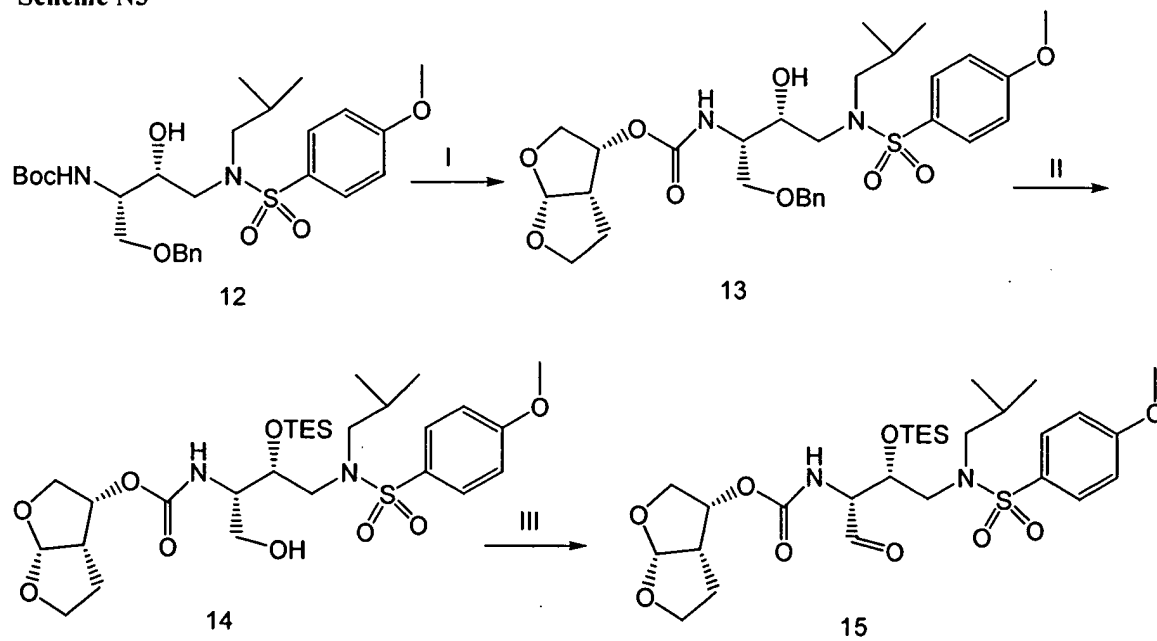
Compound 6: To a solution of compound 5 (13.5 g, 23 mmol) in ethyl acetate (135 mL) was added water (135 mL), followed by 2.5% osmium tetroxide/tert-butanol (17 mL). Sodium periodate (11.5 g) was added in portions over 2 minutes period. The mixture was stirred for 90 minutes, and was diluted with ethyl acetate. The organic layer was separated and washed with water (3x) and brine (1x), and dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 1/2) gave compound 6 as white powder (12 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.98 (1 H, s), 7.82 (2 H, m), 7.75 (2 H, m), 7.43 (2 H, m), 6.99 (2 H, m), 5.64 (1 H, m), 5.02 (2 H, m), 4.0-3.8 (9 H, m), 3.2-2.7 (7 H, m), 1.9-1.4 (3 H, m), 0.94 (6 H, m).

**Scheme N2**



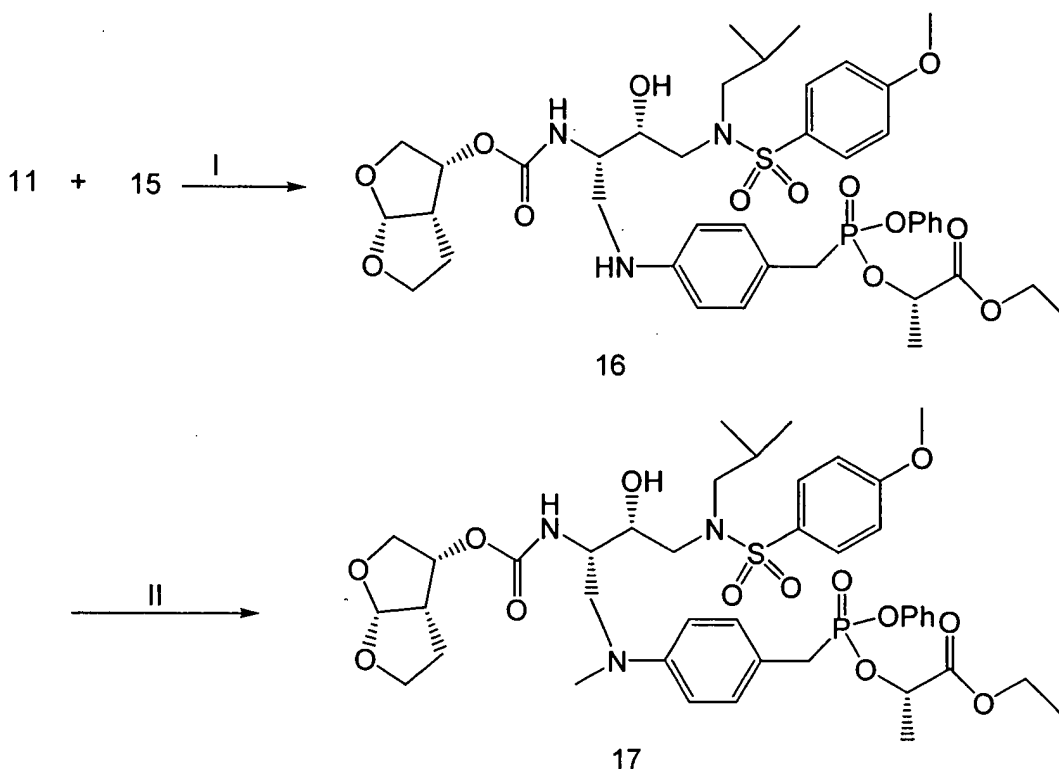
I. a.  $\text{SOCl}_2$ /toluene/60 C; b. PhOH/pyridine; II. a. NaOH/THF/ $\text{H}_2\text{O}$ ; b. HCl;  
 III. b.  $\text{SOCl}_2$ /toluene/60 C; c. ethyl lactate/pyridine; IV.  $\text{H}_2$ /10%Pd-C/EtOAc

**Scheme N3**



I. a. TFA/ $\text{CH}_2\text{Cl}_2$ ; b. bisfurancarboxonate/ $i\text{-Pr}_2\text{NEt}$ /DMAP; II. a.  $\text{Et}_3\text{SiCl}$ /imidazole/DMF;  
 b.  $\text{H}_2$ /20%Pd(OH) $_2$ -C/ $i\text{PrOH}$ ; III. Des-Martin reagent/ $\text{CH}_2\text{Cl}_2$

#### Scheme N4



I. a.  $\text{NaBH}_3\text{CN}/\text{HOAc}/\text{EtOAc}$ ; b.  $2\%\text{HF}/\text{CH}_3\text{CN}$ ;  
 II.  $\text{HCHO}/\text{NaBH}_3\text{CN}/\text{HOAc}/\text{EtOAc}$

#### Example N8

Compound 8: To the suspension of compound 7 (15.8 g, 72.5 mmol) in toluene (140 mL) was added DMF (1.9 mL), followed by thionyl chloride (53 mL, 725 mmol). The reaction mixture was heated at  $60^\circ\text{C}$  for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x), EtOAc, and  $\text{CH}_2\text{Cl}_2$  (2x) to afford a brown solid. To the solution of the brown solid in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  was added phenol (27.2 g, 290 mmol), followed by slow addition of pyridine (35 mL, 435 mmol). The reaction mixture was allowed to warm to  $25^\circ\text{C}$  and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 4/1 to 1/1) to afford compound 8 (12.5 g).

#### Example N9

Compound 9: To a solution of compound 8 (2.21 g, 6 mmol) in THF (30 mL) was added 12 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 2 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and acetic acid (343 mL, 6 mmol) was added. The aqueous phase was washed with EtOAc (3x), and then acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over MgSO<sub>4</sub>. Concentration under reduced pressure gave compound 9 as a solid (1.1 g).

#### Example N10

Compound 10: To a suspension of compound 9 (380 mg, 1.3 mmol) in toluene (2.5 mL) was added thionyl chloride (1 mL, 13 mmol), followed by DMF (1 drop). The mixture was heated at 60°C for 2 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) and CH<sub>2</sub>Cl<sub>2</sub> to give a white solid. To the solution of the above solid in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at -20°C was added ethyl lactate (294 µL, 2.6 mmol), followed by pyridine (420 µL, 5.2 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure to give a yellow solid, which was purified by flash column chromatography to generate compound 10 (427 mg).

#### Example N11

Compound 11: To a solution of compound 10 (480 mg) in EtOAc (20 mL) was added 10% Pd-C (80 mg). The reaction mixture was hydrogenated for 6 hrs. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 11 (460 mg).

#### Example N12

Compound 12 was prepared by the methods of the Examples herein.

#### Example N13

Compound 13: To a solution of compound 12 (536 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure. The liquid was coevaporated with CH<sub>2</sub>Cl<sub>2</sub> (3x) and EtOAc (3x) to give a brown solid. To the solution of above brown solid in acetonitrile (6.5 mL) at 0°C was added

bisfurancarboxylate (295 mg, 1.0 mmol), followed by diisopropylethylamine (350  $\mu$ L, 2.0 mmol) and DMAP (24 mg). The mixture was warmed to 25°C, and was stirred for 12 hrs. The mixture was diluted with EtOAc, and was washed sequentially with water (2x), 0.5 N HCl (2x), water (2x), 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1/1) afford compound 13 (540 mg).

#### Example N14

Compound 14: To a solution of compound 13 (400 mg, 0.67 mmol) in DMF (3 mL) was added imidazole (143 mg, 2.10 mmol), followed by triethylchlorosilane (224  $\mu$ L, 1.34 mmol). The mixture was stirred for 12 hours. The mixture was diluted with EtOAc, and was washed with water (5x) and brine, and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave a white solid (427 mg). To the solution of above solid in isopropanol (18 mL) was added 20% palladium(II) hydroxide on carbon (120 mg). The mixture was hydrogenated for 12 hours. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 14 (360 mg).

#### Example N15

Compound 15: To a solution of compound 14 (101 mg, 0.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added Dess-Martin periodinane (136 mg, 0.36 mmol). The mixture was stirred for 1 hour. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave compound 15 (98 mg).

#### Example N16

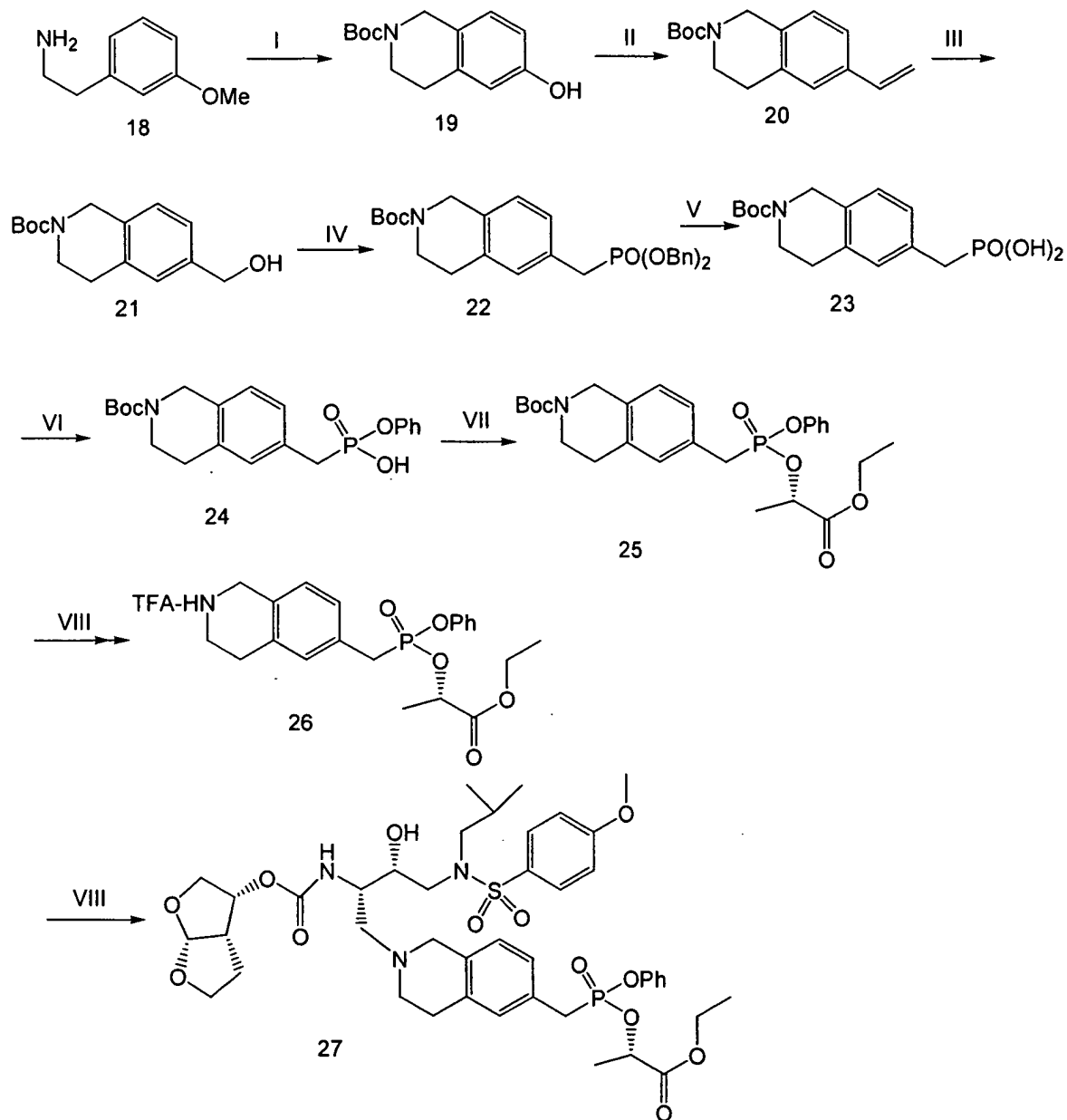
Compound 16: To a solution of compound 15 (50 mg, 0.08 mmol) in EtOAc (0.5 mL) was added compound 11 (150 mg, 0.41 mmol). The mixture was cooled to 0°C, acetic acid (19  $\mu$ L, 0.32 mmol) was added, followed by sodium cyanoborohydride (10 mg, 0.16 mmol). The mixture was warmed to 25°C, and was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with water (3x) and brine, and was dried over MgSO<sub>4</sub>. Concentration gave a oil. To the solution of above oil in acetonitrile (2.5 mL) was added 48% HF/CH<sub>3</sub>CN (0.1 mL). The mixture was stirred for 30 minutes, and was diluted with EtOAc. The organic phase was washed with water (3x) and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/3) gave compound 16 (50 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.72

(2 H, d,  $J = 8.9$  Hz), 7.15-7.05 (7 H, m), 7.30 (2 H, d,  $J = 8.9$  Hz), 6.64 (2 H, m), 5.73 (1 H, m), 5.45 (1 H, m), 5.13 (1 H, m), 4.93 (1 H, m), 4.22-3.75 (11 H, m), 3.4 (4 H, m), 3.35-2.80 (5 H, m), 2.1-1.8 (3 H, m), 1.40-1.25 (6 H, m), 0.94 (6 H, m).

#### Example N17

Compound 17: To a solution of compound 16 (30 mg, 0.04 mmol) in EtOAc (0.8 mL) was added 37% formaldehyde (26  $\mu$ L, 0.4 mmol). The mixture was cooled to 0°C, acetic acid (20  $\mu$ L, 0.4 mmol) was added, followed by sodium cyanoborohydride (22 mg, 0.4 mmol). The mixture was warmed to 25°C, and was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with water (3x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/3$ ) gave compound 17 (22 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.63 (2 H, m), 7.3-6.9 (9 H, m), 6.79 (2 H, m), 5.68 (1 H, m), 5.2 (1 H, m), 5.10 (1 H, m), 4.95 (1 H, m), 4.22 (2 H, m), 4.2-3.7 (21 H, m), 2.0-1.7 (3 H, m), 1.4-1.2 (6 H, m), 0.93 (6 H, m).

# Scheme N5



I. a. HCHO/100 C; b. HCl/100 C; c. HBr/120 C; d. Boc<sub>2</sub>O/Na<sub>2</sub>CO<sub>3</sub> II. a. Tf<sub>2</sub>NPh/Cs<sub>2</sub>CO<sub>3</sub>; b. Bu<sub>3</sub>SnCH=CH<sub>2</sub>/LiCl/PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/90 C; III. a. NaIO<sub>4</sub>/OsO<sub>4</sub>; b. NaBH<sub>4</sub>; IV. a. CBr<sub>4</sub>/PPh<sub>3</sub>; b. (BnO)<sub>2</sub>POH/Cs<sub>2</sub>CO<sub>3</sub>; V. H<sub>2</sub>/10% Pd-C; VI. a. PhOH/DCC; b. NaOH; C. HCl; VII. Ethyl lactate/BOP; VIII. TFA/CH<sub>2</sub>Cl<sub>2</sub>; VIII. compound 15/NaBH<sub>3</sub>CN/HOAc.

## Example N18

Compound 18: Compound 18 was purchased from Aldrich.

#### Example N19

Compound 19: To compound 18 (12.25 g, 81.1 mmol) was added 37% formaldehyde (6.15 mL, 82.7 mmol) slowly. The mixture was heated at 100°C for 1 hour. The mixture was cooled to 25°C, and was diluted with benzene, and was washed with water (2x). Concentration under reduced pressure gave a yellow oil. To above oil was added 20% HCl (16 mL), and the mixture was heated at 100°C for 12 hours. The mixture was basified with 40% KOH solution at 0°C, and was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, and was dried over MgSO<sub>4</sub>. Concentration gave a oil. To the oil was added 48% HBr (320 mL), and the mixture was heated at 120°C for 3 hours. Water was removed at 100°C under reduced pressure to give a brown solid. To the solution of above solid in water/dioxane (200 mL/200mL) at 0°C was added sodium carbonate (25.7 g, 243 mmol) slowly, followed by di-tert-butyl dicarbonate (19.4 g, 89 mmol). The mixture was warmed to 25°C and stirred for 12 hours. Dioxane was removed under reduced pressure, and the remaining was extracted with EtOAc (3x). The combined organic phase was washed with water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 4/1 to 3/1) gave compound 19 as white solid (13.6 g).

#### Example N20

Compound 20: To a solution of compound 19 (2.49 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added N-phenyltrifluoromethanesulfonimide (3.93 g, 11 mmol), followed by cesium carbonate (3.58 g, 11 mmol). The mixture was stirred for 48 hours. The solvent was removed under reduced pressure, and ethyl acetate was added. The reaction mixture was washed with water (3x) and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 6/1) gave a white solid (3.3 g). To the solution of above solid (2.7 g, 7.1 mmol) in DMF (40 mL) was added lithium chloride (2.11 g, 49.7 mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (100 mg, 0.14 mmol). The mixture was stirred for 3 minutes under high vacuum and recharged with nitrogen. To the above solution was added tributylvinyltin (2.07 mL, 7.1 mmol). The reaction mixture was heated at 90°C for 3 hours and cooled to 25°C. Water was added to the reaction, and the mixture was extracted with ethyl acetate (3X). The combined organic layer was washed with water (6x) and brine, and dried over MgSO<sub>4</sub>. Concentration gave an oil. The oil was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL), water (128 µL, 7.1mmol) and DBU (1 mL, 7.1 mmol) were added. The mixture was stirred for 5 minutes,

and was subjected to flash column chromatography (hexanes/EtOAc = 9/1). Compound 20 was obtained as white solid (1.43 g).

#### Example N21

Compound 21: To a solution of compound 20 (1.36 g, 5.25 mmol) in ethyl acetate (16 mL) was added water (16 mL), followed by 2.5% osmium tetroxide/*tert*-butanol (2.63 mL). Sodium periodate (2.44 g) was added in portions over 2 minutes period. The mixture was stirred for 45 minutes, and was diluted with ethyl acetate. The organic layer was separated and washed with water (3x) and brine (1x), and dried over MgSO<sub>4</sub>. Concentration gave a brown solid. To the solution of above solid in methanol (100 mL) at 0°C was added sodium borohydride. The mixture was stirred for 1 hour at 0°C, and was quenched with saturated NH<sub>4</sub>Cl (40 mL). Methanol was removed under reduced pressure, and the remaining was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave compound 21 (1.0 g).

#### Example N22

Compound 22: To a solution of compound 21 (657 mg, 2.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added a solution of tetrabromocarbon (1.276 g, 3.86 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). To the above mixture was added a solution of triphenylphosphine (673 mg, 2.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) over 30 minutes period. The mixture was stirred for 2 hours, and was concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc = 9/1) gave the bromide intermediate (549 mg). To the solution of above bromide (548 mg, 1.69 mmol) in acetonitrile (4.8 mL) was added dibenzyl phosphite (0.48 mL, 2.19 mmol), followed by cesium carbonate (828 mg, 2.54 mmol). The mixture was stirred for 48 hours, and was diluted with EtOAc. The mixture was washed with water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 3/1 to 100% EtOAc) gave compound 22 (863 mg).

#### Example N23

Compound 23: To a solution of compound 22 (840 mg) in ethanol (80 mL) was added 10% palladium on carbon (200 mg). The mixture was hydrogenated for 2 hours. The mixture

was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 23 (504 mg).

#### Example N24

Compound 24: To a solution of compound 23 (504 mg, 1.54 mmol) in pyridine (10.5 mL) was added phenol (1.45 g, 15.4 mmol), followed by DCC (1.28 g, 6.2 mmol). The mixture was heated at 65°C for 3 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 ml), and was filtered and washed with EtOAc (2x5 mL).

Concentration gave a oil, which was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{isopropanol} = 100/3$ ) to give diphenylphosphonate intermediate (340 mg). To a solution of above compound (341 mg, 0.71 mmol) in THF (1 mL) was added 0.85 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 3 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x), and then acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration under reduced pressure gave compound 24 as a solid (270 mg).

#### Example N25

Compound 25: To a solution of compound 24 (230 mg, 0.57 mmol) in DMF (2 mL) was added ethyl (s)-lactate (130  $\mu\text{L}$ , 1.14 mmol), followed by diisopropylethylamine (400  $\mu\text{L}$ , 2.28 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (504 mg, 1.14 mmol). The mixture was stirred for 14 hours, was diluted with EtOAc. The organic phase was washed with water (5x) and brine (1x), and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{isopropanol} = 100/3$ ) gave compound 25 (220 mg).

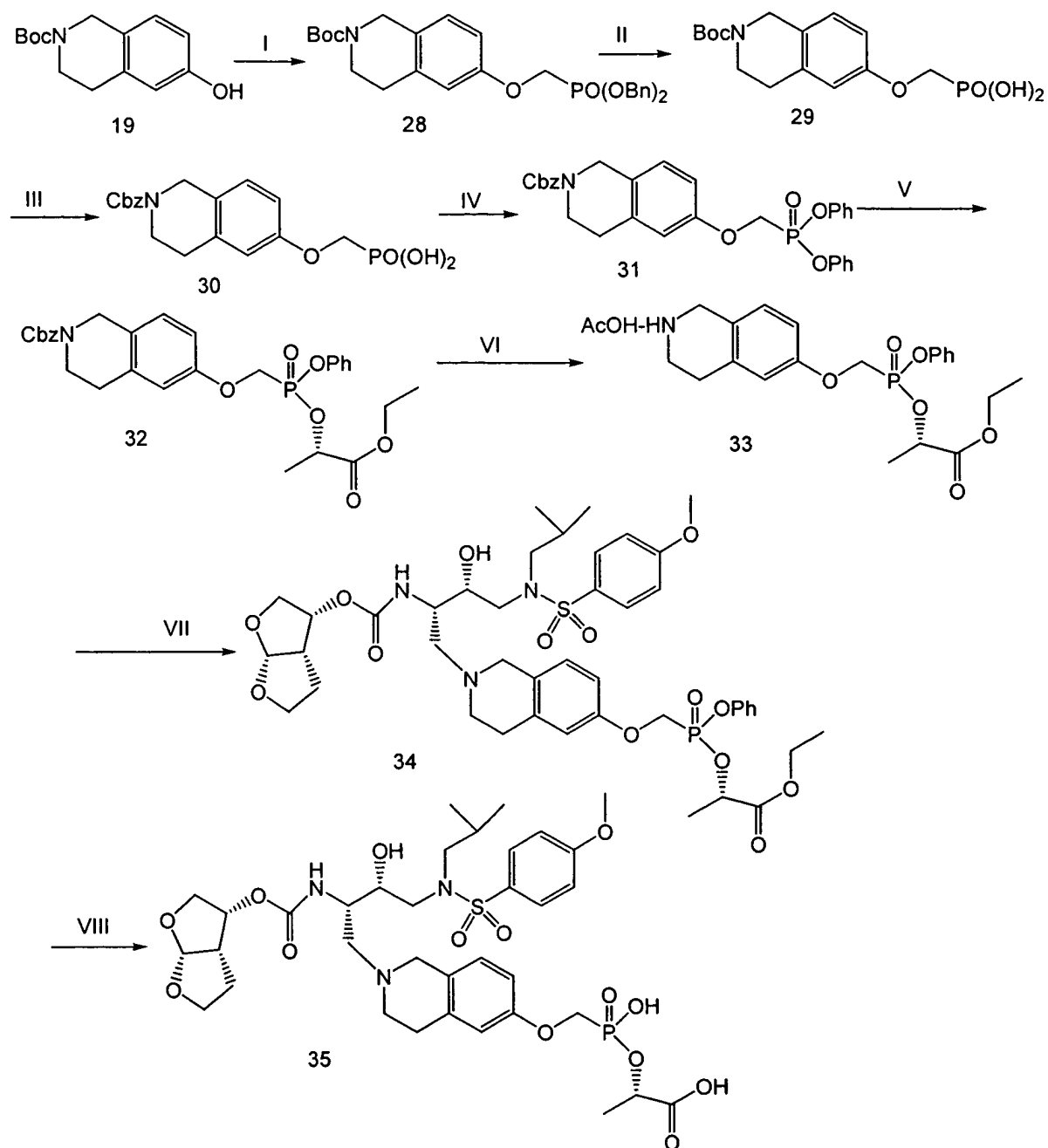
#### Example N26

Compound 26: To a solution of compound 25 (220 mg) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure. The mixture was diluted with EtOAc, and was washed with saturated sodium carbonate solution, water, and brine, and was dried over  $\text{MgSO}_4$ . Concentration gave compound 26 (170 mg).

### Example N27

Compound 27: To a solution of compound 15 (258 mg, 0.42 mmol) in EtOAc (2.6 mL) was added compound 26 (170 mg, 0.42 mmol), followed by acetic acid (75  $\mu$ L, 1.26 mmol). The mixture was stirred for 5 minutes, and sodium cyanoborohydride (53 mg, 0.84 mmol) was added. The mixture was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/4$  to  $100/6$ ) gave the intermediate (440 mg). To the solution of above compound (440 mg) in acetonitrile (10 mL) was added 48% HF/  $\text{CH}_3\text{CN}$  (0.4 mL). The mixture was stirred for 2 hours, and acetonitrile was removed under reduced pressure. The remaining was diluted with EtOAc, and was washed with water (3x) and brine (1x), and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/5$ ) gave compound 27 (120 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.70 (2 H, m), 7.27 (2 H, m), 7.15 (5 H, m), 6.95 (3 H, m), 5.73 (1 H, m), 5.6-5.4 (1 H, m), 5.16 (1 H, m), 4.96 (1 H, m), 4.22-3.60 (13 H, m), 3.42 (2 H, m), 3.4-2.6 (11 H, m), 2.1-3.8 (3 H, m), 1.39 (3 H, m), 1.24 (3 H, m), 0.84 (6 H, m).

**Scheme N6**



I.  $\text{tFOCH}_2\text{PO}(\text{OBn})_2/\text{Cs}_2\text{CO}_3$  II.  $\text{H}_2/10\% \text{ Pd-C}$ ; III. a.  $\text{TFA}/\text{CH}_2\text{Cl}_2$ ;  
 b.  $\text{CbzCl}/\text{NaOH}$ ; IV. a.  $\text{SOCl}_2/60^\circ\text{C}$ ; b.  $\text{PhOH}/\text{pyridine}$ ; V. a.  $\text{NaOH}/\text{THF}$ ;  
 b.  $\text{HCl}$ ; c.  $\text{SOCl}_2/60^\circ\text{C}$ ; d.  $\text{Ethyl (s) Lactate}/\text{pyridine}$ ; VI.  $\text{H}_2/10\% \text{ Pd-C}/\text{HOAc}$ ;  
 VII. a. compound 15/ $\text{NaBH}_3\text{CN}/\text{HOAc}$ ; b.  $2\% \text{ HF}/\text{CH}_3\text{CN}$ ;  
 VIII. esterase/ $1.0 \text{ PBS buffer}/\text{CH}_3\text{CN}/\text{DMSO}$

#### Example N28

Compound 28: To a solution of compound 19 (7.5 g, 30 mmol) in acetonitrile (420 mL) was added dibenzyl triflate (17.8 g, 42 mmol), followed by cesium carbonate (29.4 g, 90 mmol). The mixture was stirred for 2.5 hours, and was filtered. Acetonitrile was removed under reduced pressure, and the remaining was diluted with EtOAc. The mixture was washed with water (3x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) gave compound 28 (14.3 g).

#### Example N29

Compound 29: To a solution of compound 28 (14.3 g) in ethanol (500 mL) was added 10% palladium on carbon (1.45 g). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 29 (9.1 g).

#### Example N30

Compound 30: To a solution of compound 29 (9.1 g) in  $\text{CH}_2\text{Cl}_2$  (60 mL) was added trifluoroacetic acid (30 mL). The mixture was stirred for 4 hrs, and was concentrated under reduced pressure. The mixture was coevaporated with  $\text{CH}_2\text{Cl}_2$  (3x) and toluene, and was dried under high vacuum to give a white solid. The white solid was dissolved in 2.0 N NaOH solution (45 mL, 90 mmol), and was cooled to  $0^\circ\text{C}$ . To the above solution was added slowly a solution of benzyl chloroformate (6.4 mL, 45 mmol) in toluene (7 mL). The mixture was warmed to  $25^\circ\text{C}$ , and was stirred for 6 hours. 2.0 N sodium hydroxide was added to above solution until  $\text{pH} = 11$ . The aqueous was extracted with ethyl ether (3x), and was cooled to  $0^\circ\text{C}$ . To the above aqueous phase at  $0^\circ\text{C}$  was added concentrated HCl until  $\text{pH} = 1$ . The aqueous was extracted with EtOAc (3x). The combine organic layers were washed with brine, and were dried over  $\text{MgSO}_4$ . Concentration gave compound 30 (11.3 g) as a white solid.

#### Example N31

Compound 31: To the suspension of compound 30 (11.3 g, 30 mmol) in toluene (150 mL) was added thionyl chloride (13 mL, 180 mmol), followed by DMF (a few drops). The reaction mixture was heated at  $65^\circ\text{C}$  for 4.5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x) to afford a brown solid. To the solution of the

brown solid in  $\text{CH}_2\text{Cl}_2$  (120 mL) at  $0^\circ\text{C}$  was added phenol (11.28 g, 120 mmol), followed by slow addition of pyridine (14.6 mL, 180 mmol). The reaction mixture was allowed to warm to  $25^\circ\text{C}$  and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 3/1 to 1/1) to afford compound 31 (9.8 g).

#### Example N32

Compound 32: To a solution of compound 31 (9.8 g, 18.5 mmol) in THF (26 mL) was added 20.3 mL of 1.0 N NaOH solution. The mixture was stirred at  $25^\circ\text{C}$  for 2.5 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x). The aqueous phase was cooled to  $0^\circ\text{C}$ , and was acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration under reduced pressure gave a solid (8.2 g). To a suspension of above solid (4.5 g, 10 mmol) in toluene (50 mL) was added thionyl chloride (4.4 mL, 60 mmol), followed by DMF (0.2 mL). The mixture was heated at  $70^\circ\text{C}$  for 3.5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a white solid. To the solution of the above solid in  $\text{CH}_2\text{Cl}_2$  (40 mL) at  $0^\circ\text{C}$  was added ethyl (s)-lactate (2.3 mL, 20 mmol), followed by pyridine (3.2 mL, 40 mmol). The mixture was warmed to  $25^\circ\text{C}$  and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was diluted with EtOAc. The organic phase was washed with 1 N HCl, water, and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) gave compound 32 (4.1 g).

#### Example N33

Compound 33: To a solution of compound 32 (3.8 g, 6.9 mmol) in EtOAc/EtOH (30 mL/30 mL) was added 10% palladium on carbon (380 mg), followed by acetic acid (400  $\mu\text{L}$ , 6.9 mmol). The mixture was hydrogenated for 3 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 33 (3.5 g).

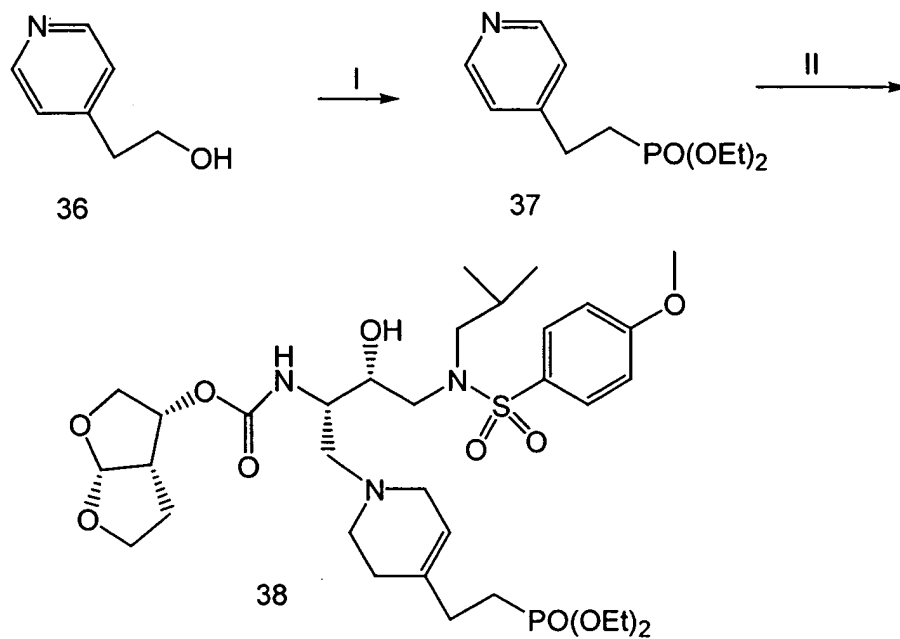
#### Example N34

Compound 34: To a solution of compound 15 (1.70 g, 2.76 mmol) in EtOAc (17 mL) was added compound 33 (3.50 g, 6.9 mmol). The mixture was stirred for 5 minutes, and was cooled to 0°C, and sodium cyanoborohydride (347 mg, 5.52 mmol) was added. The mixture was stirred for 6 hrs. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/6) gave the intermediate (3.4 g). To the solution of above compound (3.4 g) in acetonitrile (100 mL) was added 48% HF/ CH<sub>3</sub>CN (4 mL). The mixture was stirred for 2 hours, and acetonitrile was removed under reduced pressure. The remaining was diluted with EtOAc, and was washed with saturated sodium carbonate, water (3x), and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/5) gave compound 34 (920 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (2 H, m), 7.38-7.19 (5 H, m), 6.92 (3 H, m), 6.75 (2 H, m), 5.73 (1 H, m), 5.57-5.35 (1 H, m), 5.16 (2 H, m), 4.5 (2 H, m), 4.2-3.6 (13 H, m), 3.25-2.50 (11 H, m), 2.0-1.8 (3 H, m), 1.5 (3 H, m), 1.23 (3 H, m), 0.89 (6 H, m).

#### Example N35

Compound 35: To a solution of compound 34 (40 mg) in CH<sub>3</sub>CN /DMSO (1 mL/0.5 mL) was added 1.0 M PBS buffer (5 mL), followed by esterase (200 µL). The mixture was heated at 40°C for 48 hours. The mixture was purified by reverse phase HPLC to give compound 35 (11 mg).

### Scheme N7



I. a.  $\text{SOCl}_2$ /toluene/60 °C; b.  $\text{P}(\text{OEt})_3$ /toluene/120 °C;  
II. a. compound 14/ $\text{Tf}_2\text{O}$ ; b.  $\text{NaBH}_4$ /EtOH/HOAc; c. 2% HF/ $\text{CH}_3\text{CN}$

### Example N36

Compound 36: Compound 36 was purchased from Aldrich.

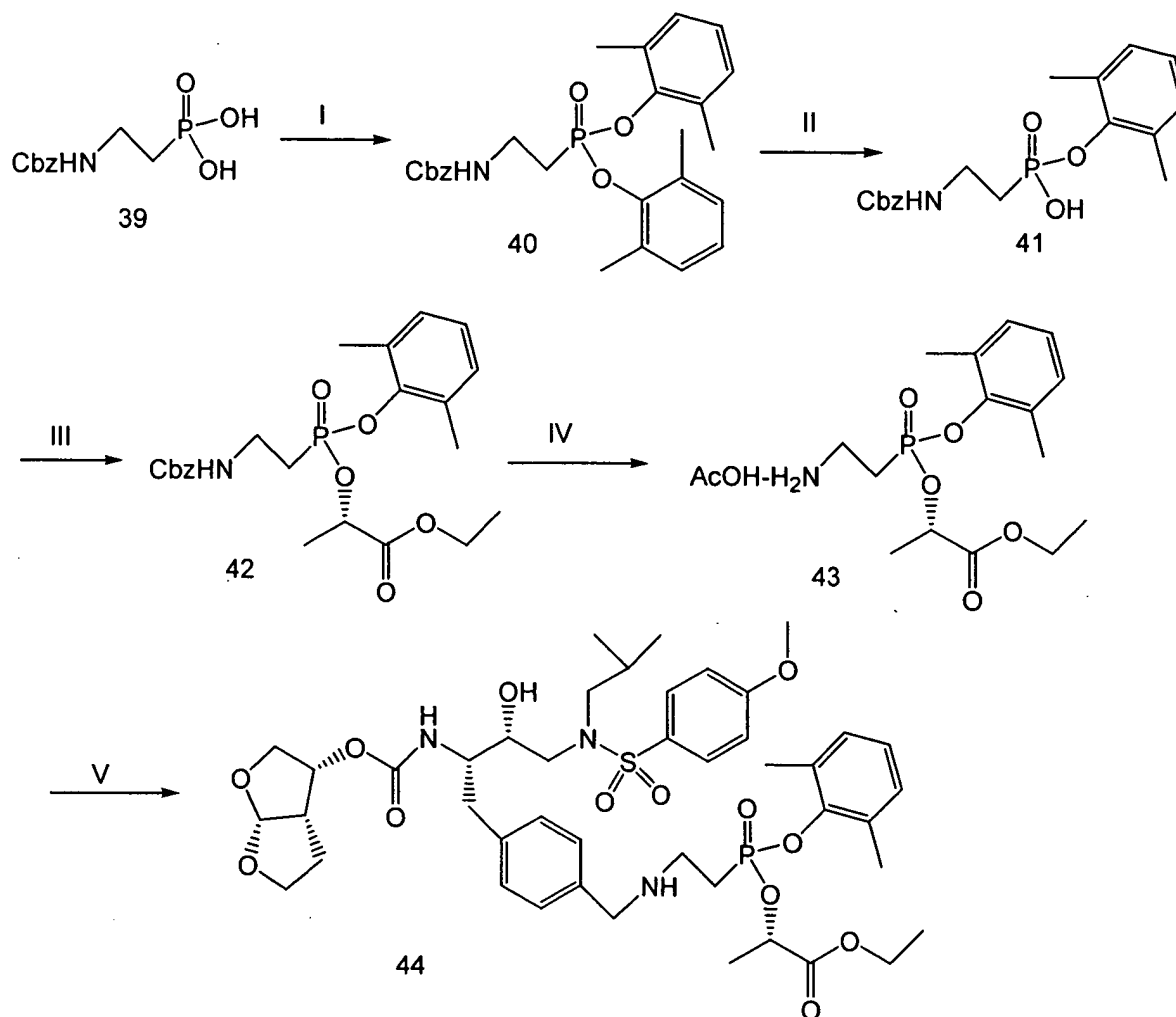
### Example N37

Compound 37: To a solution of compound 36 (5.0 g, 40 mmol) in chloroform (50 mL) was added thionyl chloride (12 mL) slowly. The mixture was heated at 60 °C for 2.5 hours. The mixture was concentrated under reduced pressure to give a yellow solid. To the suspension of above solid (5.2 g, 37 mmol) in toluene (250 mL) was added triethyl phosphite (19 mL, 370 mmol). The mixture was heated at 120 °C for 4 hours, and was concentrated under reduced pressure to give a brown solid. The solid was dissolved in EtOAc, and was basified with 1.0 N NaOH. The organic phase was separated and was washed with water (2x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2$ /iPrOH = 9/1) gave compound 37 (4.8 g).

### Example N38

Compound 38: To a solution of compound 14 (100 mg, 0.16 mmol) and compound 37 (232 mg, 0.74 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) at  $-40^\circ\text{C}$  was added triflic anhydride (40  $\mu\text{L}$ , 0.24 mmol) slowly. The mixture was warmed to  $25^\circ\text{C}$  slowly, and was stirred for 12 hours. The mixture was concentrated, and was diluted with EtOH/EtOAc (2 mL/0.4 mL). To the above solution at  $0^\circ\text{C}$  was added sodium borohydride (91 mg) in portions. The mixture was stirred at  $0^\circ\text{C}$  for 3 hours, and was diluted with EtOAc. The mixture was washed with saturated sodium bicarbonate, water, and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatograph ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/5$  to  $100/10$ ) gave the intermediate (33 mg). To the solution of above intermediate in acetonitrile (2.5 mL) was added 48% HF/  $\text{CH}_3\text{CN}$  (0.1 mL). The mixture was stirred for 30 minutes, and was diluted with EtOAc. The organic solution was washed with 0.5 N sodium hydroxide, water, and brine, was dried over  $\text{MgSO}_4$ . Purification by reverse HPLC gave compound 38 (12 mg):  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.72 (2 H, d,  $J = 8.9$  Hz), 7.02 (2 H, d,  $J = 8.9$  Hz), 5.70 (1 H, m), 5.45 (1 H, m), 5.05 (1 H, m), 4.2-3.4 (19 H, m), 3.4-2.8 (5 H, m), 2.45-2.20 (4 H, m), 2.15-1.81 (5 H, m), 1.33 (6 H, m), 0.89 (6 H, m).

# Scheme N8



I. a.  $\text{SOCl}_2$ /toluene/60 °C; b. ArOH/pyridine; II. a. NaOH/THF/ $\text{H}_2\text{O}$ ; b. HCl;  
 III. b.  $\text{SOCl}_2$ /toluene/60 °C; c. ethyl lactate/pyridine; IV.  $\text{H}_2$ /10%Pd-C/EtOAc/HOAc;  
 V. a. compound 6/ $\text{MgSO}_4$ ; b. HOAc/ $\text{NaCNBH}_3$

## Example N39

Compound 39 was prepared by the methods of the previous Examples.

## Example N40

Compound 40: To the suspension of compound 39 (4.25 g, 16.4 mmol) in toluene (60 mL) was added thionyl chloride (7.2 mL, 99 mmol), followed by DMF (a few drops). The reaction mixture was heated at 65°C for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x) to afford a brown solid. To the solution of the

brown solid in  $\text{CH}_2\text{Cl}_2$  (60 mL) at  $0^\circ\text{C}$  was added 2,6-dimethylphenol (8.1 g, 66 mmol), followed by slow addition of pyridine (8 mL, 99 mmol). The reaction mixture was allowed to warm to  $25^\circ\text{C}$  and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 3/1 to 1/1) afforded compound 40 (1.38 g).

#### Example N41

Compound 41: To a solution of compound 40 (1.38 g, 1.96 mmol) in THF (6 mL) was added 3.55 mL of 1.0 N NaOH solution. The mixture was stirred at  $25^\circ\text{C}$  for 24 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x). The aqueous phase was cooled to  $0^\circ\text{C}$ , and was acidified with concentrated HCl until  $\text{pH} = 1$ . The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration under reduced pressure gave compound 41 as a white solid (860 mg).

#### Example N42

Compound 42: To a suspension of compound 41 (1.00 g, 2.75 mmol) in toluene (15 mL) was added thionyl chloride (1.20 mL, 16.5 mmol), followed by DMF (3 drops). The mixture was heated at  $65^\circ\text{C}$  for 5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a brown solid. To the solution of the above solid in  $\text{CH}_2\text{Cl}_2$  (11 mL) at  $0^\circ\text{C}$  was added ethyl (s)-lactate (1.25, 11 mmol), followed by pyridine (1.33 mL, 16.6 mmol). The mixture was warmed to  $25^\circ\text{C}$  and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was diluted with EtOAc. The organic phase was washed with 1 N HCl, water, and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 1.5/1 to 1/1) gave compound 42 (470 mg).

#### Example N43

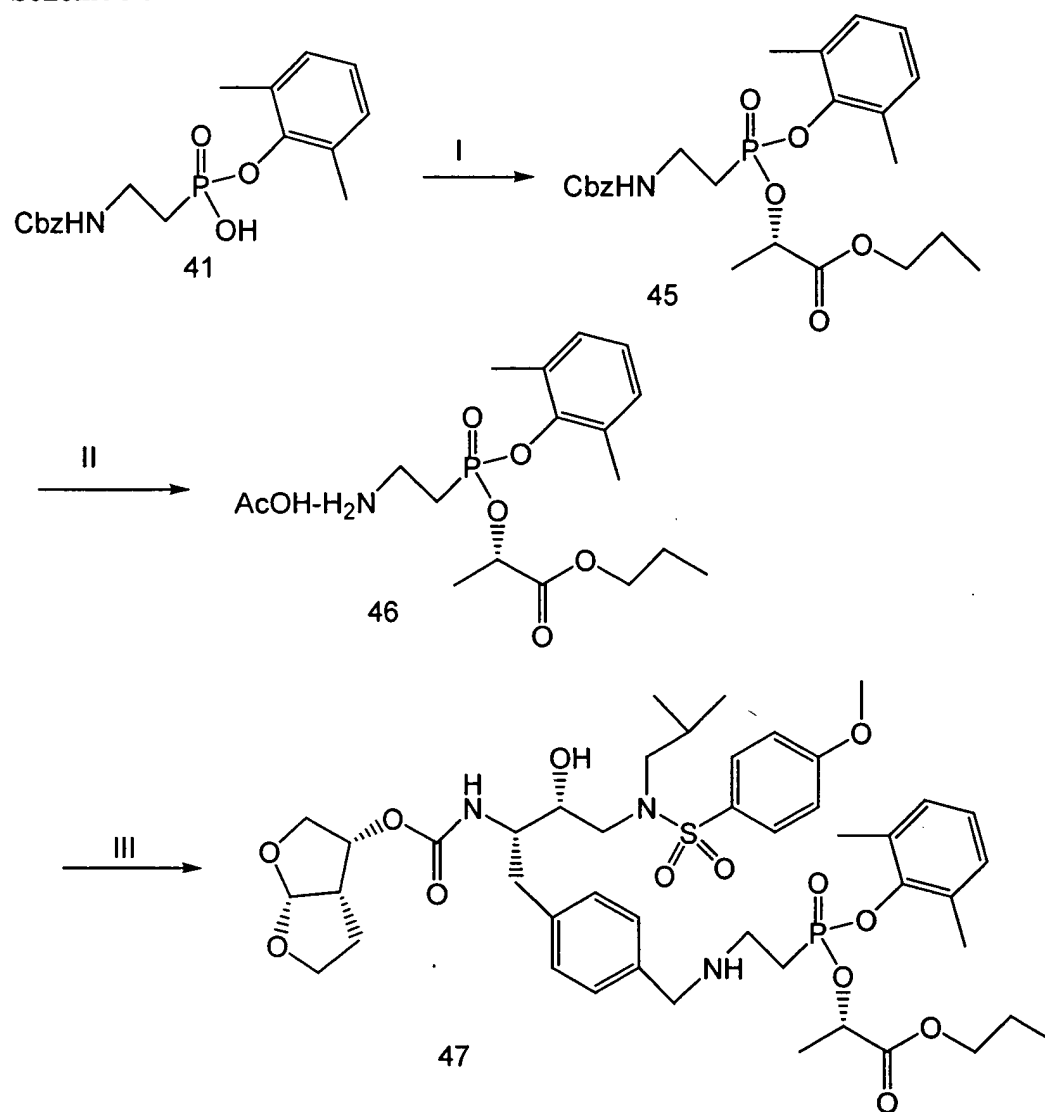
Compound 43: To a solution of compound 42 (470 mg) in EtOH (10 mL) was added 10% palladium on carbon (90 mg), followed by acetic acid (150  $\mu\text{L}$ ). The mixture was

hydrogenated for 6 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 43 (400 mg).

#### Example N44

Compound 44: To a solution of compound 6 (551 mg, 0.93 mmol) in 1,2-dichloroethane (4 mL) was added compound 43 (400 mg, 1.0 mmol), followed by  $\text{MgSO}_4$  (1 g). The mixture was stirred for 3 hours, and acetic acid (148  $\mu\text{L}$ ) and sodium cyanoborohydride (117 mg, 1.86 mmol) were added sequentially. The mixture was stirred for 1 hour. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (EtOAc to EtOAc/EtOH = 9/1) gave compound 44. Compound 44 was dissolved in  $\text{CH}_2\text{Cl}_2$  (25 mL), and trifluoroacetic acid (100  $\mu\text{L}$ ) was added. The mixture was concentrated to give compound 44 as a TFA salt (560 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74 (2 H, m), 7.39 (2 H, m), 7.20 (2 H, m), 7.03 (5 H, m), 5.68 (1 H, m), 5.43 (1 H, m), 5.01 (1 H, m), 4.79 (1 H, m), 4.35-4.20 (4 H, m), 4.18-3.4 (11 H, m), 3.2-2.6 (9 H, m), 2.30 (6 H, m), 1.82 (1 H, m), 1.70 (2 H, m), 1.40-1.18 (6 H, m), 0.91 (6 H, m).

## Scheme N9



- I. b. SOCl<sub>2</sub>/toluene/60 °C; c. propyl (S)-lactate/pyridine;  
 II. H<sub>2</sub>/10% Pd-C/EtOAc/HOAc;  
 III. a. compound 6/MgSO<sub>4</sub>; b. HOAc/NaCNBH<sub>3</sub>

## Example N45

Compound 45: To a suspension of compound 41 (863 mg, 2.4 mmol) in toluene (13 mL) was added thionyl chloride (1.0 mL, 14.3 mmol), followed by DMF (3 drops). The mixture was heated at 65 °C for 5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a brown solid. To the solution of the above solid in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C was added propyl (S)-lactate (1.2 mL, 9.6 mmol), followed by

triethylamine (2.0 mL, 14.4 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was diluted with EtOAc. The organic phase was washed with water and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1.5/1 to 1/1) gave compound 45 (800 mg).

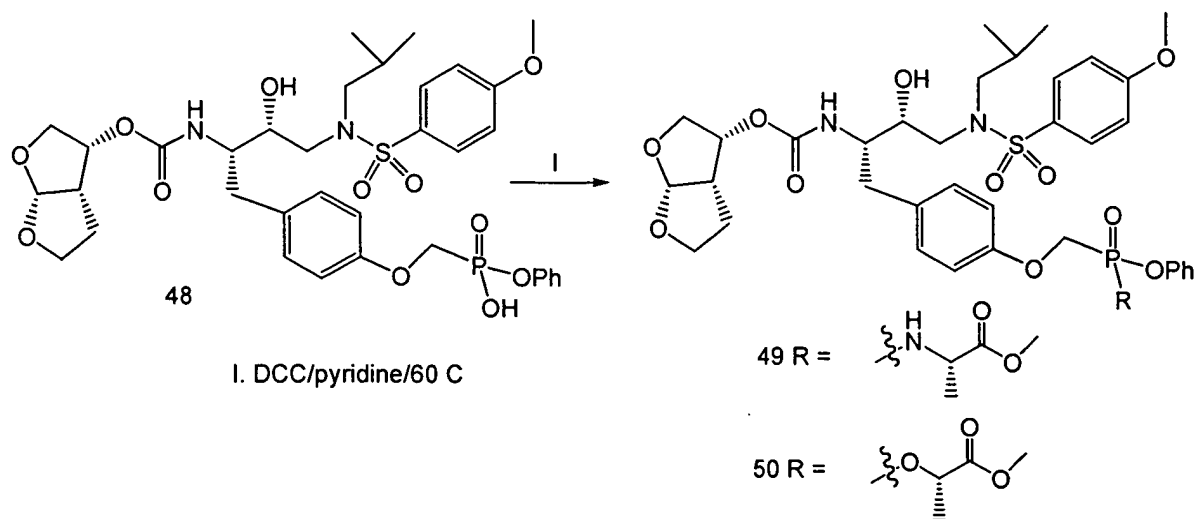
#### Example N46

Compound 46: To a solution of compound 45 (785 mg) in EtOH (17 mL) was added 10% palladium on carbon (150 mg), followed by acetic acid (250 µL). The mixture was hydrogenated for 16 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 46 (700 mg).

#### Example N47

Compound 47: To a solution of compound 6 (550 mg, 0.93 mmol) in 1,2-dichloroethane (4 mL) was added compound 43 (404 mg, 1.0 mmol), followed by MgSO<sub>4</sub> (1 g). The mixture was stirred for 3 hours, and acetic acid (148 µL) and sodium cyanoborohydride (117 mg, 1.86 mmol) were added sequentially. The mixture was stirred for 1 hour. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (EtOAc to EtOAc/EtOH = 9/1) gave compound 47. Compound 47 was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL), and trifluoroacetic acid (100 µL) was added. The mixture was concentrated to give compound 47 as a TFA salt (650 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.74 (2 H, m), 7.41 (2 H, m), 7.25-7.1 (2 H, m), 7.02 (5 H, m), 5.65 (1 H, m), 5.50 (1 H, m), 5.0-4.75 (2 H, m), 4.25-4.05 (4 H, m), 4.0-3.4 (11 H, m), 3.2-2.6 (9 H, m), 2.31 (6 H, m), 1.82-1.51 (3 H, m), 1.45-1.2 (5 H, m), 0.93 (9 H, m).

## Scheme N10



### Example N48

Compound 48 was made by the methods of the previous Examples.

### Example N49

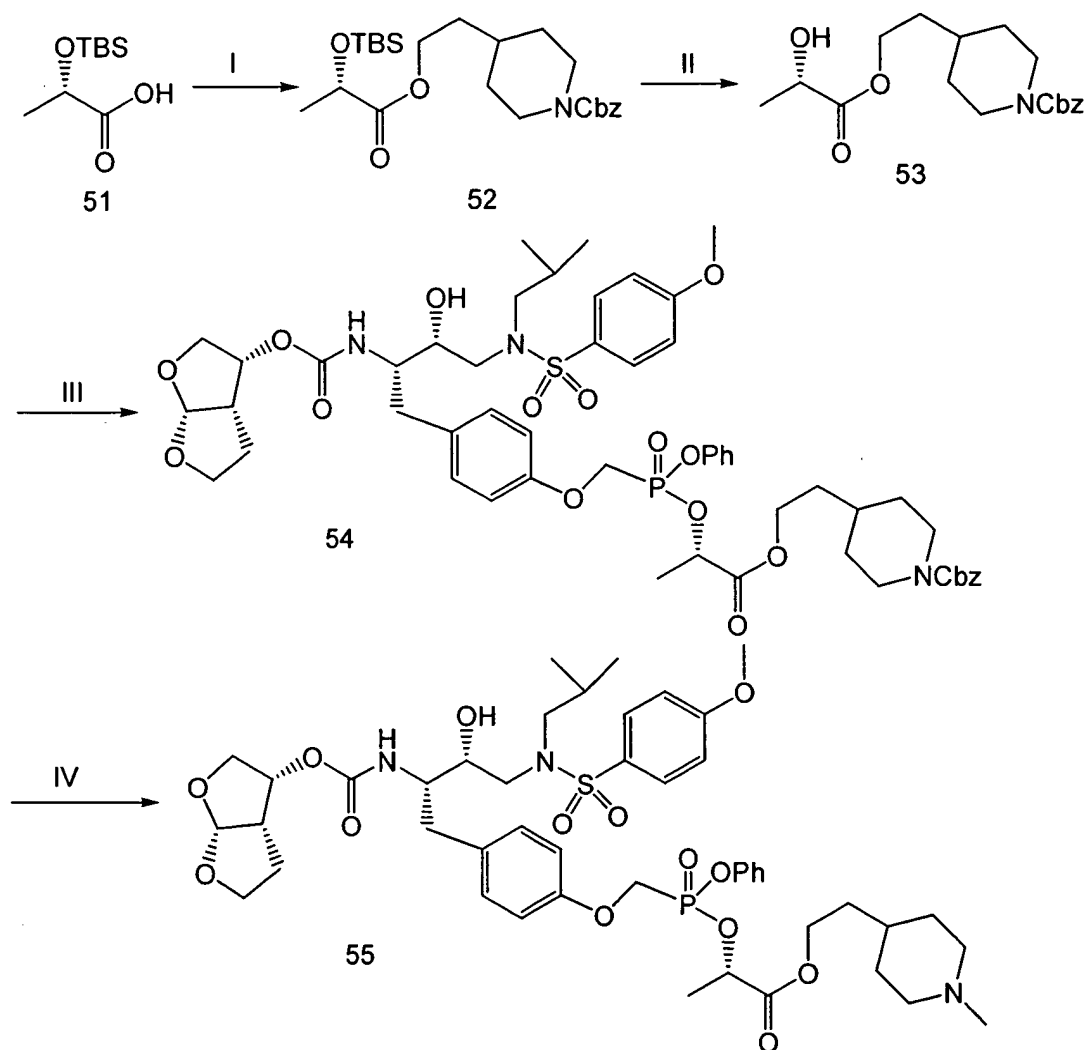
Compound 49: To a solution of compound 48 (100 mg, 0.13 mmol) in pyridine (0.75 mL) was added L-alanine methyl ester hydrochloride (73 mg, 0.52 mmol), followed by DCC (161 mg, 0.78 mmol). The mixture was heated at 60°C for 1 hour. The mixture was diluted with EtOAc, and was washed with 0.2 N HCl, water, 5% sodium bicarbonate, and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/5) gave compound 49 (46 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (2 H, m), 7.38-7.18 (7 H, m), 7.03 (2 H, m), 6.89 (2 H, m), 5.68 (1 H, m), 5.05 (1 H, m), 4.95 (1 H, m), 4.30 (3 H, m), 4.0-3.6 (12 H, m), 3.2-2.8 (7 H, m), 1.84-1.60 (3 H, m), 1.38 (3 H, m), 0.93 (6 H, m).

### Example N50

Compound 50: To a solution of compound 48 (100 mg, 0.13 mmol) in pyridine (0.75 mL) was added methyl (s)-lactate (41 mg, 0.39 mmol), followed by DCC (81 mg, 0.39 mmol). The mixture was heated at 60°C for 2 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 mL), and was filtered. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/5) gave compound 50 (83 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.74 (2 H, m), 7.38-7.14 (7 H, m), 7.02 (2 H, m), 6.93 (2 H, m), 5.67 (1 H, m), 5.18 (1 H, m), 5.04 (1

H, m), 4.92 (1 H, m), 4.5 (2 H, m), 4.0-3.68 (12 H, m), 3.2-2.75 (7 H, m), 1.82 (1 H, m), 1.75-1.50 (5 H, m), 0.93 (6 H, m).

#### Scheme N11



I. Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ROH/*i*Pr<sub>2</sub>NEt;  
 II. 15% HF/CH<sub>3</sub>CN; III. Compound 48/DCC/pyridine/60 °C; IV. a. H<sub>2</sub>/10%Pd-C;  
 b. NaBH<sub>3</sub>CN/HCHO/HOAc

#### Example N51

Compound 51: To a solution of benzyl (S)-lactate (4.0 g, 20 mmol) in DMF (40 mL) was added imidazole (2.7 g, 20 mmol), followed by tert-butyldimethylsilyl chloride (3.3 g, 22 mmol). The mixture was stirred for 14 hours, and diluted with EtOAc. The organic phase was washed

with 1.0 N HCl solution (2x), water (2x), and brine (1x), and dried over MgSO<sub>4</sub>. Concentration gave the lactate intermediate (6.0 g). To the solution of the above intermediate in EtOAc (200 mL) was added 10% Palladium on carbon (700 mg). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 minutes, and was filtered through a pad of celite. Concentration gave compound 51 (3.8 g).

#### Example N52

Compound 52: To a solution of compound 51 (1.55 g, 7.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added 4-benzyloxycarbonylpiperidineethanol (2.00 g, 7.6 mmol), followed by benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (4.74 g, 9.1 mmol) and diisopropylethylamine (1.58 mL, 9.1 mmol). The mixture was stirred for 14 hours, and dichloromethane was removed. The mixture was diluted with EtOAc, and was washed with brine, and dried with MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 10/1) gave compound 52 (1.50 g).

#### Example N53

Compound 53: To a solution of compound 52 (1.50 g) in CH<sub>3</sub>CN was added 58% HF/CH<sub>3</sub>CN (5 mL). The mixture was stirred for 30 minutes, and acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1/1) gave compound 53 (1.00 g).

#### Example N54

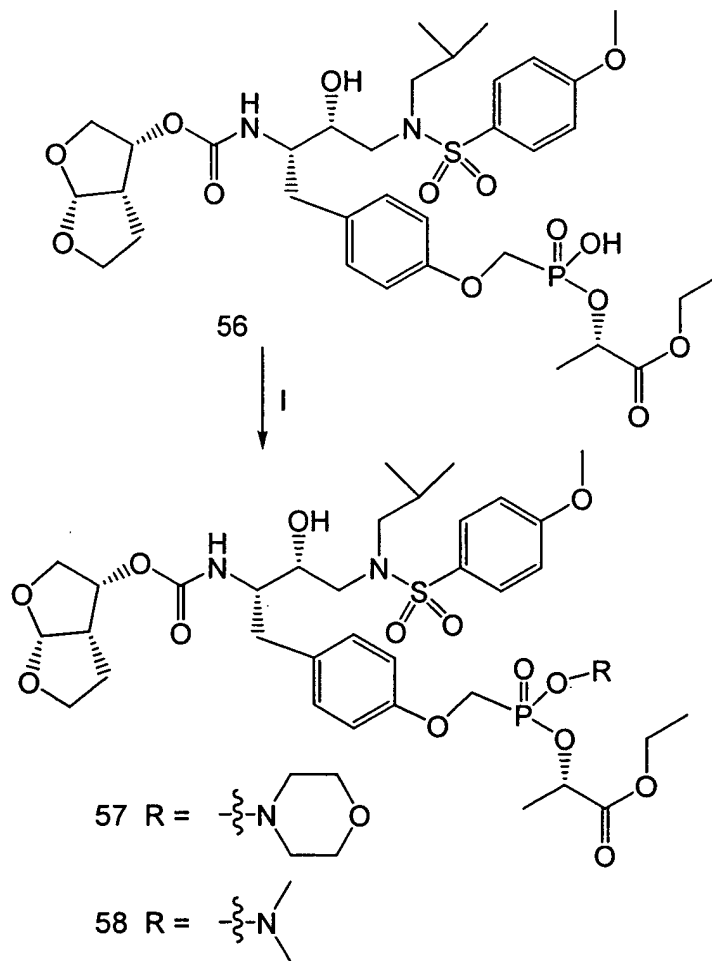
Compound 54: To a solution of compound 48 (769 mg, 1.0 mmol) in pyridine (6.0 mL) was added compound 53 (1.0 g, 3.0 mmol), followed by DCC (618 mg, 3.0 mmol). The mixture was heated at 60°C for 2 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 mL), and was filtered. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/4) gave compound 54 (630 mg).

#### Example N55

Compound 55: To a solution of compound 54 (630 mg, 0.58 mmol) in EtOAc (30 mL) was added 10% Palladium on carbon (63 mg), followed by acetic acid (80 µL). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 minutes, and was filtered

through a pad of celite. Concentration gave the intermediate. To the solution of the above intermediate in EtOAc (10 mL) was added 37% formaldehyde (88  $\mu$ L, 1.18 mmol), followed by acetic acid (101  $\mu$ L, 1.77 mmol). The mixture was cooled to 0°C, and sodium cyanoborohydride (74 mg, 1.18 mmol) was added. The mixture was stirred at 25°C for 80 minutes, and was diluted with EtOAc. The mixture was washed with water and brine, and was dried over MgSO<sub>4</sub>. Concentration gave compound 55 as a white solid (530 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.74 (2 H, m), 7.40-7.15 (7 H, m), 7.03 (2 H, m), 6.92 (2 H, m), 5.66 (1 H, m), 5.20-5.00 (3 H, m), 4.58–4.41 (2 H, m), 4.16 (2 H, m), 4.0-3.7 (9 H, m), 3.4-2.6 (14 H, m), 1.90-1.50 (13 H, m), 0.92 (6 H, m).

#### Scheme N12



I. R<sub>2</sub>NOH/DCC/pyridine

#### Example N56

Compound 56 was made by the methods of the previous Examples.

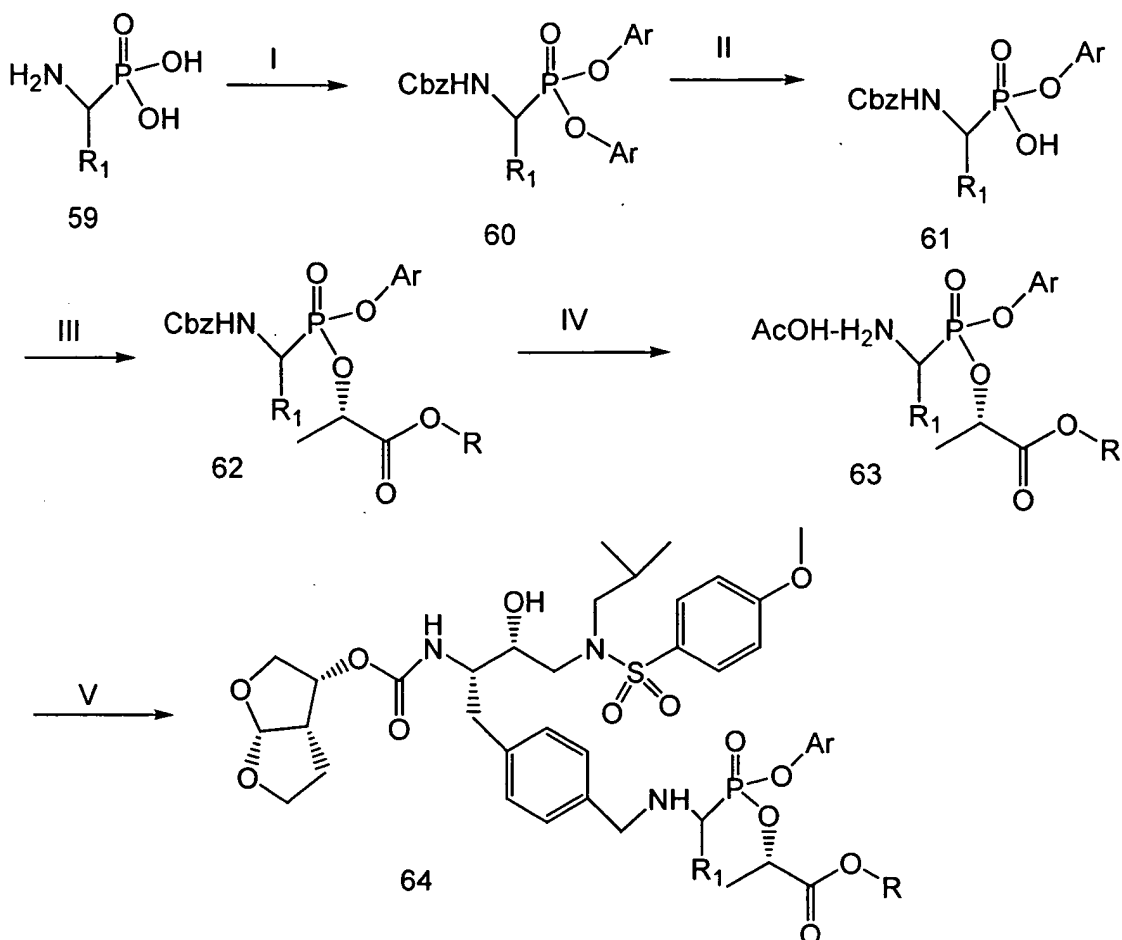
#### Example N57

Compound 57: To a solution of compound 56 (100 mg, 0.12 mmol) in pyridine (0.6 mL) was added N-hydroxymorpholine (50 mg, 0.48 mmol), followed by DCC (99 mg, 0.48 mmol). The mixture was stirred for 14 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc, and was filtered. Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/5$ ) gave compound 57 (53 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (2 H, d,  $J = 8.6$  Hz), 7.15 (2 H, d,  $J = 7.6$  Hz), 6.99 (2 H, d,  $J = 8.8$  Hz), 6.90 (2 H, m), 5.67 (1 H, m), 5.18 (1 H, m), 5.05 (1 H, m), 4.95 (1 H, m), 4.58-4.38 (2 H, m), 4.21 (2 H, m), 4.02-3.80 (13 H, m), 3.55-3.38 (2 H, m), 3.2-2.78 (9 H, m), 1.9-1.8 (1 H, m), 1.8-0.95 (5 H, m), 1.29 (3 H, m), 0.93 (6 H, m).

#### Example N58

Compound 58: To a solution of compound 56 (100 mg, 0.12 mmol) in pyridine (0.6 mL) was added N,N-dimethylhydroxylamine hydrochloride (47 mg, 0.48 mmol), followed by DCC (99 mg, 0.48 mmol). The mixture was stirred for 6 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc, and was filtered. Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/5$ ) gave compound 58 (35 mg).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (2 H, d,  $J = 8.9$  Hz), 7.15 (2 H, d,  $J = 8.2$  Hz), 6.99 (2 H, d,  $J = 8.4$  Hz), 6.89 (2 H, m), 5.65 (1 H, d,  $J = 5.2$  Hz), 5.15 (1 H, m), 4.98 (2 H, m), 4.42 (2 H, m), 4.18 (2 H, m), 4.0-3.6 (9 H, m), 3.2-2.7 (13 H, m), 1.92-1.45 (6 H, m), 1.25 (3 H, m), 0.90 (6 H, m).

# **Scheme N13**



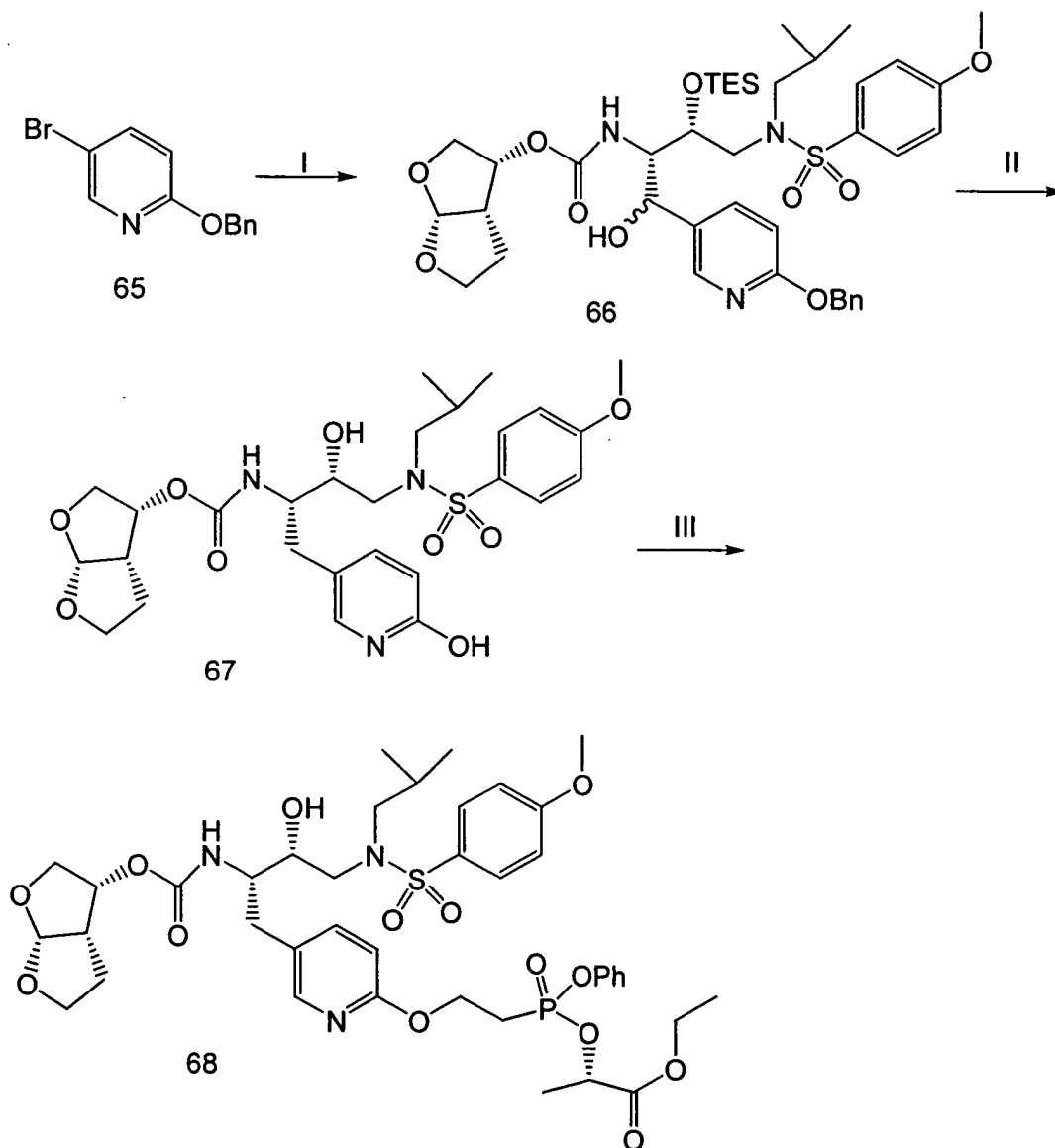
R = Me, Et, Pr, i-Pr; R<sub>1</sub> = H, Me, Et, i-Pr; Ar = phenyl, 2, 6-dimethylphenyl

I. a. CbzCl/NaOH; b..SOCl<sub>2</sub>/toluene/60 C; c. ArOH/pyridine; II. a.NaOH/THF/H<sub>2</sub>O; b. HCl;  
 III. a.SOCl<sub>2</sub>/toluene/60 C; b.alkyll lactate/pyridine; IV. H<sub>2</sub>/10%Pd-C/EtOAc/HOAc;  
 V. a. compound 6/MgSO<sub>4</sub>; b. HOAc/NaCNBH<sub>3</sub>

Aminomethylphosphonic acid 59 is protected as benzyl carbamate. The phosphonic acid is treated with thionyl chloride to generate dichloridate, which reacts with phenol or 2,6-dimethylphenol to give compound 60. Compound 60 is hydrolyzed with sodium hydroxide, followed by acidification to afford monoacid 61. Monoacid 61 is treated with thionyl chloride to generate monochloridate, which reacts with different alkyl (s)-lactates to form compound 62. Compound 62 is hydrogenated with 10%Pd-C in the presence of acetic acid to give compound

63. Compound 63 reacts with aldehyde 6 in the presence of  $\text{MgSO}_4$  to form imine, which is reduced with sodium cyanoborohydride to generate compound 64.

**Scheme N14**



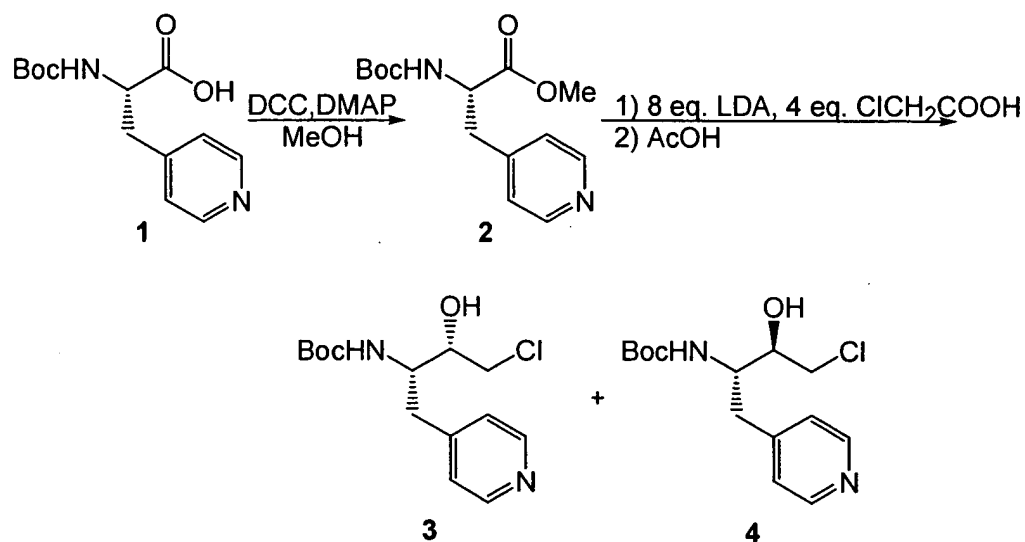
I. a. *n*-BuLi; b. compound 15; II.  $\text{H}_2/10\%\text{Pd-C}/\text{HOAc}$ ; IV.  $\text{PPh}_3/\text{DEAD}$

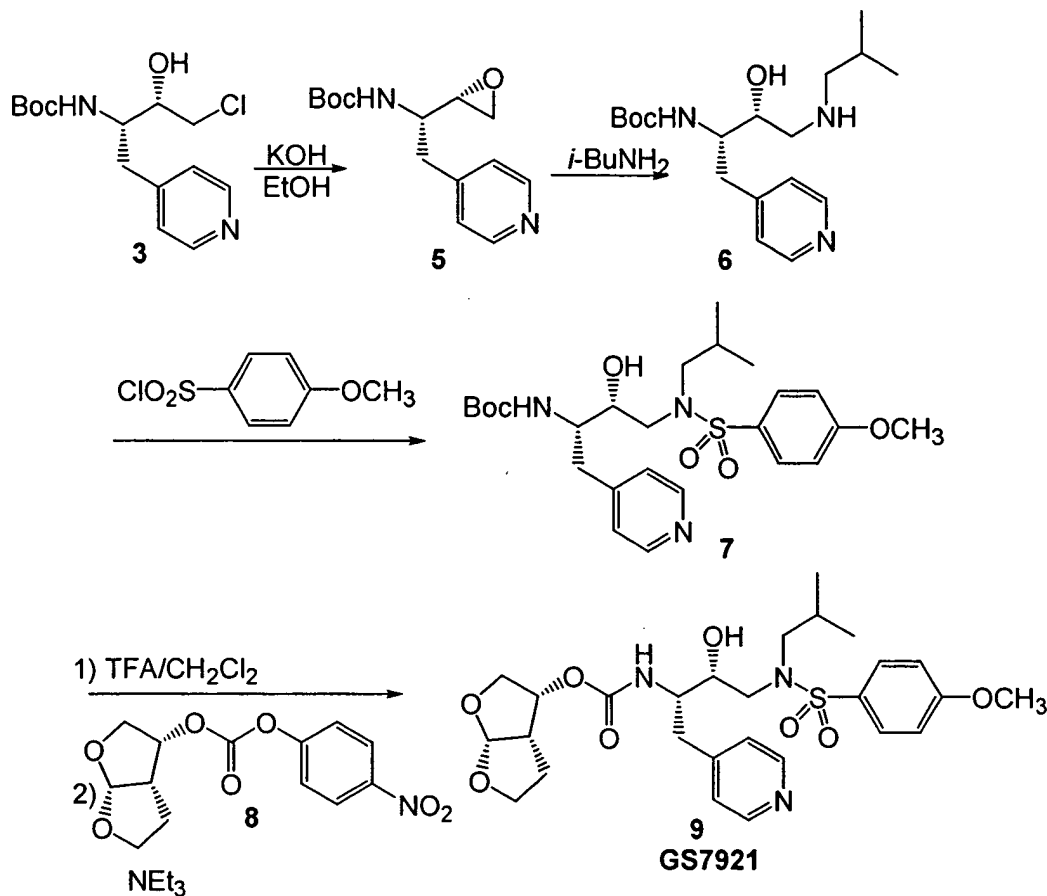
Compound 65 is prepared from 2-hydroxy-5-bromopyridine by alkylation. *J. Med. Chem.* 1992, 35, 3525. Compound 65 is treated with *n*-Butyl lithium to generate aryl lithium, which reacts with aldehyde 15 to form compound 66. *J. Med. Chem.* 1994, 37, 3492. Compound 66 is

hydrogenated with 10%Pd-C in the presence of acetic acid to give compound 67. *J. Med. Chem.* 2000, 43, 721. Compound 68 is prepared from compound 67 with corresponding alcohol under Mitsunobu reaction conditions. *Bioorg. Med.Chem. Lett.* 1999, 9, 2747

### Example Section O

#### Scheme O1





### Example O1

Methyl 2-(S)-(dimethylethoxycarbonylamino)-3-(4-pyridyl)propanoate (2): A solution of N-tert-Butoxycarbonyl-4-pyridylalanine (1, 9.854 g, 37 mmol, Peptech), 4-dimethylaminopyridine (4.52 g, 37 mmol, Aldrich), and dicyclohexylcarbodiimide (15.30 g, 74.2 mmol, Aldrich) in methanol (300 mL) was stirred at  $0^\circ\text{C}$  for 2 h and at room temperature for 12 h. After the solids were removed by filtration, the filtrate was concentrated under reduced pressure. More dicyclohexylurea was removed by repeated trituration of the concentrated residue in EtOAc followed by filtration. The residue was chromatographed on silica gel to afford the methyl ester 2 (9.088 g, 88%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.53 (d, 2H,  $J = 5.7$  Hz), 7.09 (d, 2H,  $J = 5.7$  Hz), 5.04 (br, 1H), 4.64 (br, 1H), 3.74 (s, 3H), 3.16 (dd, 1H,  $J = 13.5$  and 5.7 Hz), 3.02 (dd, 1H,  $J = 13.5$  and 6.3 Hz), 1.42 (s, 9H); MS (ESI) 281 (M+H).

### Example O2

1-Chloro-3-(S)-(dimethylethoxycarbonylamino)-4-(4-pyridyl)-2-(S)-butanol (3): A solution of diisopropylamine (37.3 mL, 266 mmol, Aldrich) in THF (135 mL) was stirred at –

78°C as a solution of *n*-butyllithium (102 mL of 2.3 M solution and 18 mL of 1.4 M solution 260 mmol, Aldrich) in hexane was added. After 10 min, the cold bath was removed and stirred the solution for 10 min at the ambient temperature. The solution was cooled at -78°C again and stirred as a solution of chloroacetic acid (12.255 g, 130 mmol, Aldrich) in THF (50 mL) was added over 20 min. After the solution was stirred for 15 min, this dianion solution was transferred to a stirred solution of the methyl ester **2** (9.087 g, 32.4 mmol) in THF (100 mL) at 0°C over 15 min. The resulting yellow slurry was stirred at 0°C for 10 min and cooled at -78°C. A solution of acetic acid (29 mL, 507 mmol, Aldrich) in THF (29 mL) was added quickly to the slurry and the resulting slurry was stirred at -78°C for 30 min, at 0°C for 30 min, and at room temperature for 15 min. The resulting slurry was dissolved in saturated NaHCO<sub>3</sub> solution (750 mL) and EtOAc (500 mL). The separated aqueous layer was extracted with EtOAc (300 mL x 2) and the combined organic fractions were washed with water (750 mL x 2) and saturated NaCl solution (250 mL). The resulting solution was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure.

A solution of the residue in THF (170 mL) and water (19 mL) was stirred at 0°C as NaBH<sub>4</sub> (3.375 g, 89.2 mmol, Aldrich) was added. After 30 min, the solution was evaporated under reduced pressure and the residue was dissolved in EtOAc, acidified with aqueous NaHSO<sub>4</sub>, and then neutralized by adding saturated aqueous NaHCO<sub>3</sub> solution. The separated aqueous fraction was extracted with EtOAc (100 mL) and the combined organic fractions were washed with water (500 mL) and saturated NaCl solution (100 mL). The solution was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was chromatographed on silica gel to afford the chlorohydrin **3** and **4** (4.587 g, 47%) as a mixture of two diastereomers (3~4:1). The obtained mixture was recrystallized from EtOAc-hexane twice to obtain pure desired diastereomer **3** (2.444 g, 25%) as yellow crystals: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.53 (d, 2H, *J* = 5.7 Hz), 7.18 (d, 2H, *J* = 5.7 Hz), 4.58 (br, 1H), 3.94 (m, 1H), 3.87 (br, 1H), 3.75-3.54 (m, 2H), 3.05 (dd, 1H, *J* = 13.8 and 3.9 Hz), 2.90 (dd, 1H, *J* = 13.8 and 8.4 Hz), 1.36 (s, 9H); MS (ESI) 301 (M+H).

### Example O3

The epoxide **5**: A solution of the chlorohydrin **3** (1.171 g, 3.89 mmol) in ethanol (39 mL) was stirred at room temperature as 0.71 M KOH in ethanol (6.6 mL) was added. After 1.5 h, the mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (60

mL) and water (60 mL). The separated aqueous fraction was extracted with EtOAc (60 mL) and the combined organic fractions were washed with saturated NaCl solution, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to obtain the epoxide (1.058 g, quantitative): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.52 (d, 2H, *J* = 6.0 Hz), 7.16 (d, 2H, *J* = 6.0 Hz), 4.57 (d, 1H, *J* = 7.8 Hz), 3.76 (br, 1H), 3.02-2.92 (m, 2H), 2.85-2.79 (m, 2H), 2.78-2.73 (m, 1H), 1.37 (s, 9H); MS (ESI) 265 (M+H).

#### Example O4

The hydroxy-amine 6: A solution of the epoxide 5 obtained above and *i*-BuNH<sub>2</sub> (3.9 mL, 39.2 mmol, Aldrich) in 58 mL of *i*-PrOH was stirred at 65°C for 2 h and the solution was concentrated under reduced pressure. The residual *i*-PrOH was removed by dissolving the residue in toluene and concentration of the solution twice: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.51 (d, 2H, *J* = 6.0 Hz), 7.18 (d, 2H, *J* = 6.0 Hz), 4.70 (d, 1H, *J* = 9.6 Hz), 3.86 (br, 1H), 3.46 (q, 1H, *J* = 5.8 Hz), 3.06 (dd, 1H, *J* = 14.1 and 3.9 Hz), 2.79 (dd, 1H, *J* = 14.1 and 9.0 Hz), 2.76-2.63 (m, 3H), 2.43 (m, 2H, *J* = 6.9 Hz), 1.73 (m, 1H, *J* = 6.6 Hz), 1.36 (s, 9H), 0.93 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 6.6 Hz); MS (ESI) 338 (M+H).

#### Example O5

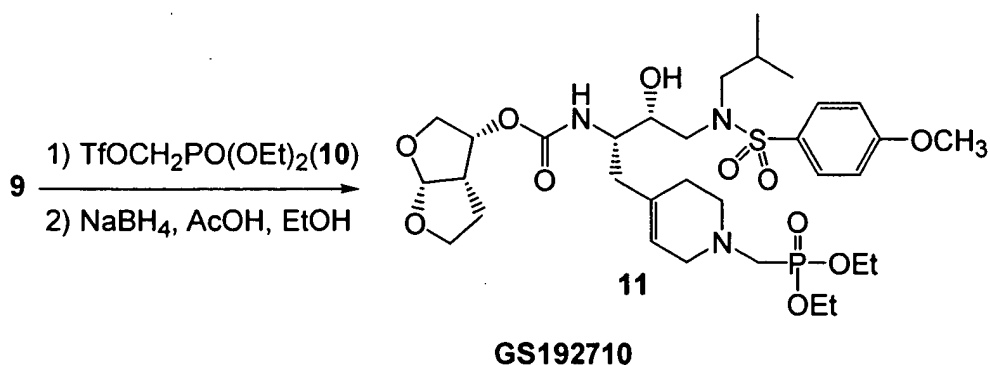
The sulfoamide 7: A solution of the crude 6 and *p*-methoxybenzene sulfonyl chloride (890 mg, 4.31 mmol, Aldrich) in CH<sub>2</sub>Cl<sub>2</sub> (24 mL) was stirred at 0°C for 2 h and at room temperature for 13 h. The solution was washed with saturated NaHCO<sub>3</sub> solution and the aqueous washing was extracted with CH<sub>2</sub>Cl<sub>2</sub> (60 mL). After the combined organic fractions were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to obtain the sulfoamide 7 (1.484 g, 75%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.51 (d, 2H, *J* = 5.7 Hz), 7.73 (d, 2H, *J* = 8.7 Hz), 7.21 (d, 2H, *J* = 5.7 Hz), 7.00 (d, 2H, *J* = 8.7 Hz), 4.68 (d, 1H, *J* = 8.1 Hz), 4.08 (br, 1H), 3.88 (s, 3H), 3.83 (br, 2H), 3.09 (d, 2H, *J* = 5.1 Hz), 3.06-2.80 (m, 4H), 1.85 (m, 1H, *J* = 7.0 Hz), 1.34 (s, 9H), 0.92 (d, 3H, *J* = 6.3 Hz), 0.89 (d, 3H, *J* = 6.6 Hz); MS (ESI) 508 (M+H).

#### Example O6

The bisfurancarbamate 9: A solution of the sulfoamide 7 (1.484 g, 2.92 mmol) and trifluoroacetic acid (6.8 mL, 88.3 mmol, Aldrich) in CH<sub>2</sub>Cl<sub>2</sub> (18 mL) was stirred at room

temperature for 2 h. After the solution was evaporated under reduced pressure, the residue was dissolved in acetonitrile (10 mL) and toluene (10 mL), and evaporated to dryness twice to result crude amine as TFA salt. A solution of the crude amine, dimethylaminopyridine (72 mg, 0.59 mmol, Aldrich), diisopropylethylamine (2.55 mL, 14.6 mmol, Aldrich) in acetonitrile was stirred at 0°C as the bisfurancarboxylate **8** (907 mg, 3.07 mmol, obtained from Azar) was added in portion. The solution was stirred at 0°C for 1 h and at room temperature for 19 h, and concentrated under reduced pressure. The residue was dissolved in EtOAc (60 mL) and washed with saturated NaHCO<sub>3</sub> solution (60 mL). After the aqueous washing was extracted with EtOAc (60 mL), the combined organic fractions were washed with saturated NaHCO<sub>3</sub> (60 mL) and saturated NaCl solution (60 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the carbamate **9** (1.452 g, 88%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.50 (d, 2H, *J* = 5.7 Hz), 7.72 (d, 2H, *J* = 8.7 Hz), 7.19 (d, 2H, *J* = 5.7 Hz), 7.01 (d, 2H, *J* = 8.7 Hz), 5.65 (d, 1H, *J* = 5.1 Hz), 5.12 (d, 1H, *J* = 9.3 Hz), 5.02 (q, 1H, *J* = 6.7 Hz), 4.01-3.77 (m, 4H), 3.88 (s, 3H), 3.76-3.63 (m, 2H), 3.18-2.76 (m, 7H), 1.95-1.77 (m, 1H), 1.77-1.56 (m, 2H), 1.56-1.41 (m, 1H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.90 (d, 3H, *J* = 6.9 Hz); MS (ESI) 564 (M+H).

## Scheme O2

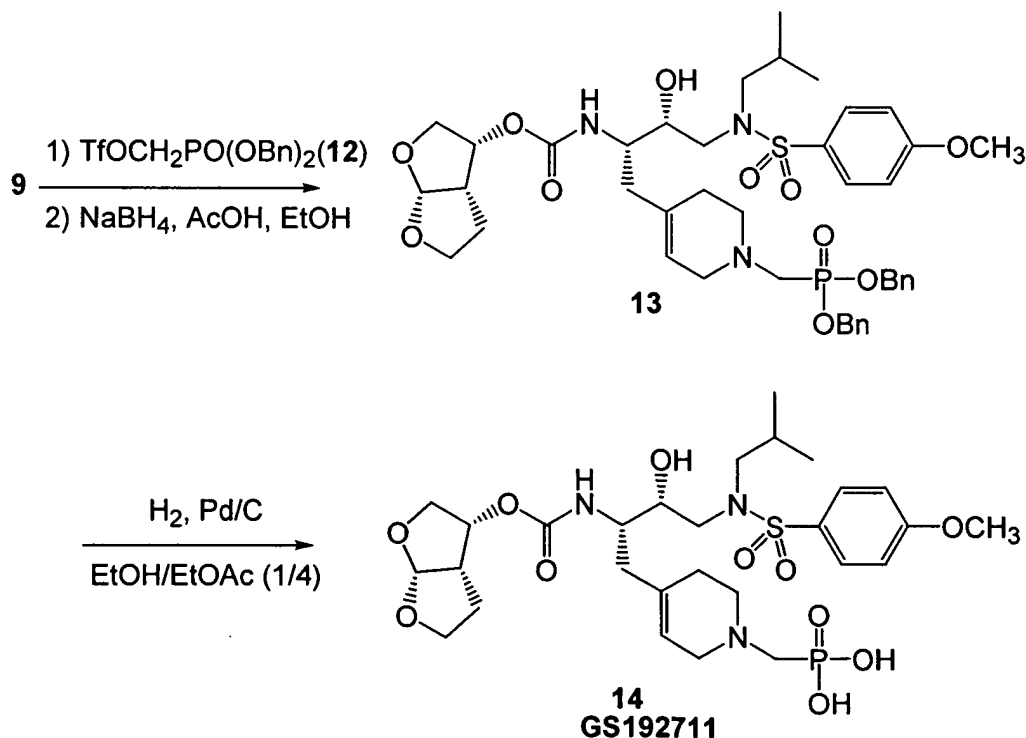


## Example O7

The tetrahydropyridine-diethyl phosphonate **11**: A solution of the pyridine **9** (10.4 mg, 0.018 mmol) and the triflate **10** (8.1 mg, 0.027 mmol, in acetone-d<sub>6</sub> (0.75 mL) was stored at room temperature for 9 h and the solution was concentrated under reduced pressure: <sup>31</sup>P NMR (acetone-d<sub>3</sub>) δ 14.7; MS (ESI) 714 (M<sup>+</sup>). The concentrated crude pyridinium salt was dissolved in ethanol (2 mL) and stirred at room temperature as NaBH<sub>4</sub> (~10 mg, Aldrich) was added

occasionally over 4 h. To the mixture was added a solution of acetic acid (0.6 mL, Aldrich) in ethanol (3 mL) until the pH of the mixture became 3~4. More NaBH<sub>4</sub> and acetic acid were added until the reaction was completed. The mixture was carefully concentrated under reduced pressure and the residue was dissolved in saturated NaHCO<sub>3</sub> solution (10 mL). The product was extracted using EtOAc (10 mL x 3) and washed with saturated NaCl solution, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the product **11** (8.5 mg, 64%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (d, 2H, *J* = 8.7 Hz), 7.00 (d, 2H, *J* = 8.7 Hz), 5.71 (d, 1H, *J* = 5.1 Hz), 5.41 (br, 1H), 5.15-5.08 (m, 1H), 5.00 (br, 1H), 4.14 (dq, 4H, *J* = 7.2 Hz), 4.06-3.94 (m, 2H), 3.88 (s, 3H), 3.92-3.80 (m, 2H), 3.75 (dd, 1H, *J* = 9.6 and 6.6 Hz), 3.79-3.61 (m, 1H), 3.24-2.94 (m, 6H), 2.85 (d, 2H, *J* = 11.7 Hz), 2.88-2.76 (m, 2H), 2.75-2.63 (m, 1H), 2.38-2.29 (m, 1H), 2.24-2.2.12 (m, 2H), 2.12-1.78 (m, 4H), 1.30 (t, 6H, *J* = 7.1 Hz), 0.94 (d, 3H, *J* = 6.6 Hz), 0.91 (d, 3H, *J* = 6.3 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 24.6; MS (ESI) 740 (M+Na).

### Scheme O3



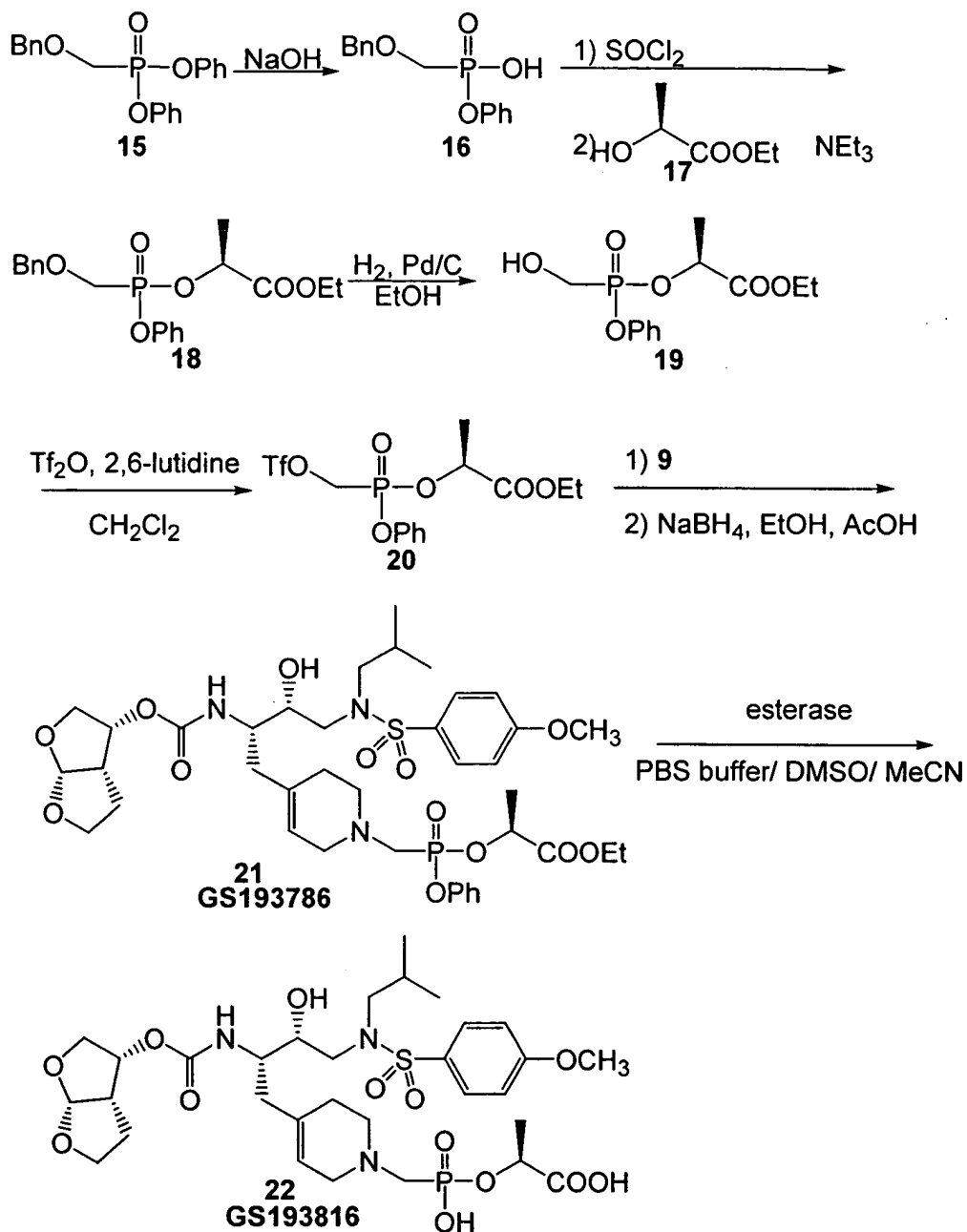
### Example O8

The tetrahydropyridine-dibenzyl phosphonate **13**: The compound **13** was obtained by the same procedure as described for compound **11** using the pyridine **9** (10.0 mg, 0.018 mmol) and the triflate **12** (9.4 mg, 0.022 mmol). The product **13** was purified by preparative TLC to afford the dibenzyl phosphonate **13** (8.8 mg, 59%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (d, 2H,  $J = 8.7$  Hz), 7.35 (s, 10H), 7.00 (d, 2H,  $J = 8.7$  Hz), 5.65 (d, 1H<sub>2</sub>H,  $J = 5.1$  Hz), 5.39 (br, 1H), 5.15-4.92 (m, 6H), 4.03-3.77 (m, 6H), 3.77-3.62 (m, 2H), 3.56 (br, 1H), 3.24-2.62 (m, 9H), 2.32 (d, 1H,  $J = 13.5$  Hz), 2.24-1.75 (m, 6H), 0.94 (d, 3H,  $J = 6.6$  Hz), 0.89 (d, 3H,  $J = 6.3$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.5; MS (ESI) 842 (M+H).

### Example O9

The phosphonic acid **14**: A mixture of the dibenzyl phosphonate **13** (8.8 mg, 0.011 mmol) and 10% Pd/C in EtOAc (2 mL) and EtOH (0.5 mL) was stirred under  $\text{H}_2$  atmosphere for 10 h at room temperature. After the mixture was filtered through celite, the filtrate was concentrated to dryness to afford the product **14** (6.7 mg, quantitative):  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.76 (d, 2H,  $J = 9.0$  Hz), 7.10 (d, 2H,  $J = 9.0$  Hz), 5.68 (d, 1H,  $J = 5.1$  Hz), 5.49 (br, 1H), 5.11 (m, 1H), 3.90 (s, 3H), 4.04-3.38 (m, 10H), 3.22 (d, 2H,  $J = 12.9$  Hz), 3.18-3.00 (m, 2H), 2.89-2.75 (m, 2H), 2.68-2.30 (m, 3H), 2.21-1.80 (m, 4H), 0.92 (d, 3H,  $J = 6.3$  Hz), 0.85 (d, 3H,  $J = 6.3$  Hz);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  6.29; MS (ESI) 662 (M+H).

#### Scheme O4



#### Example O10

Diphenyl benzyloxymethylphosphonate 15: To a solution of diphenylphosphite (46.8 g, 200 mmol, Aldrich) in acetonitrile (400 mL) (at ambient temperature) was added potassium carbonate (55.2 g, 400 mmol) followed by the slow addition of benzyl chloromethyl ether (42 mL, 300 mmol, about 60%, Fluka). The mixture was stirred overnight, and was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water, saturated

NaCl, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated. The crude product was chromatographed on silica gel to afford the benzylether (6.8 g, 9.6%) as a colorless liquid.

#### Example O11

Monoacid 16: To a solution of diphenyl benzyloxymethylphosphonate 15 (6.8 g, 19.1 mmol) in THF (100 mL) at room temperature was added 1N NaOH in water (21 mL, 21 mmol). The solution was stirred 3 h. The THF was evaporated under reduced pressure and water (100 mL) was added. The aqueous solution was cooled to  $0^\circ\text{C}$ , neutralized to pH 7 with 3N HCl and washed with EtOAc. The aqueous solution was again cooled to  $0^\circ\text{C}$ , acidified with 3N HCl to pH 1, saturated with sodium chloride, and extracted with EtOAc. The organic layer was washed with brine and dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated, then co-evaporated with toluene to yield the monoacid (4.0 g, 75%) as a colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.28-7.09 (m, 10H), 4.61 (s, 2H), 3.81 (d, 2H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.8.

#### Example O12

Ethyl lactate phosphonate 18: To a solution of monoacid 16 (2.18 g, 7.86 mmol) in anhydrous acetonitrile (50 mL) under a nitrogen atmosphere was slowly added thionyl chloride (5.7 mL, 78 mmol). The solution was stirred in a  $70^\circ\text{C}$  oil bath for three hours, cooled to room temperature and concentrated. The residue was dissolved in anhydrous dichloromethane (50 mL), and this solution cooled to  $0^\circ\text{C}$  and stirred under a nitrogen atmosphere. To the stirring solution was added ethyl (S)-(-)-lactate (2.66 mL, 23.5 mmol) and triethylamine (4.28 mL, 31.4 mmol). The solution was warmed to room temperature and allowed to stir for one hour. The solution was diluted with ethyl acetate, washed with water, brine, citric acid and brine again, dried ( $\text{MgSO}_4$ ), filtered through Celite, concentrated under reduced pressure and chromatographed on silica gel using 30% ethylacetate in hexane. The two diastereomers were pooled together.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.40-7.16 (m, 20H), 5.18-5.13 (m, 2H), 4.73 (s, 2H), 4.66 (d, 2H), 4.28-4.11 (m, 5H), 4.05 (d, 2H), 3.95 (d, 2H), 1.62 (d, 3H), 1.46 (d, 3H), 1.30-1.18 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.6, 17.7.

#### Example O13

Ethyl lactate phosphonate with free alcohol 19: Ethyl lactate phosphonate 18 was dissolved in EtOH (50 mL) and under a nitrogen atmosphere 10% Pd-C (approximately 20 wt %)

was added. The nitrogen atmosphere was replaced with hydrogen (1 atm) and the suspension stirred for two hours. 10% Pd-C was again added (20 wt %) and the suspension stirred five hours longer. Celite was added, the reaction mixture was filtered through Celite and the filtrate was concentrated to afford 1.61 g (71% from monoacid 16) of the alcohol as a colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.40-7.16 (m, 10H), 5.16-5.03 (m, 2H), 4.36-4.00 (m, 8H), 1.62 (d, 3H), 1.46 (d, 3H), 1.30-1.22 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.3, 20.0.

#### Example O14

Triflate 20: To a solution of ethyl lactate phosphonate with free alcohol 19 (800 mg, 2.79 mmol) in anhydrous dichloromethane (45 mL) chilled to  $-40^\circ\text{C}$  under a nitrogen atmosphere was added triflic anhydride (0.516 mL, 3.07 mmol) and 2-6 lutidine (0.390 mL, 3.34 mmol). The solution was stirred for 3 hr, then warmed to  $-20^\circ\text{C}$  and stirred one hour longer. 0.1 equivalents of triflic anhydride and 2-6 lutidine were then added and stirring was resumed for 90 minutes more. The reaction mixture was diluted with ice-cold dichloromethane, washed with ice-cold water, washed with ice-cold brine and the organic layer was dried ( $\text{MgSO}_4$ ) and filtered. The filtrate was concentrated and chromatographed on silica gel using 30% EtOAc in hexane as eluent to afford 602 mg (51%) of the triflate diastereomers as a slightly pink, transparent liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45-7.31 (m, 4H), 7.31-7.19 (m, 6H), 5.15-4.75 (m, 6H), 4.32-4.10 (4H), 1.62 (d, 3H), 1.50 (d, 3H), 1.30-1.22 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  10.3, 8.3.

#### Example O15

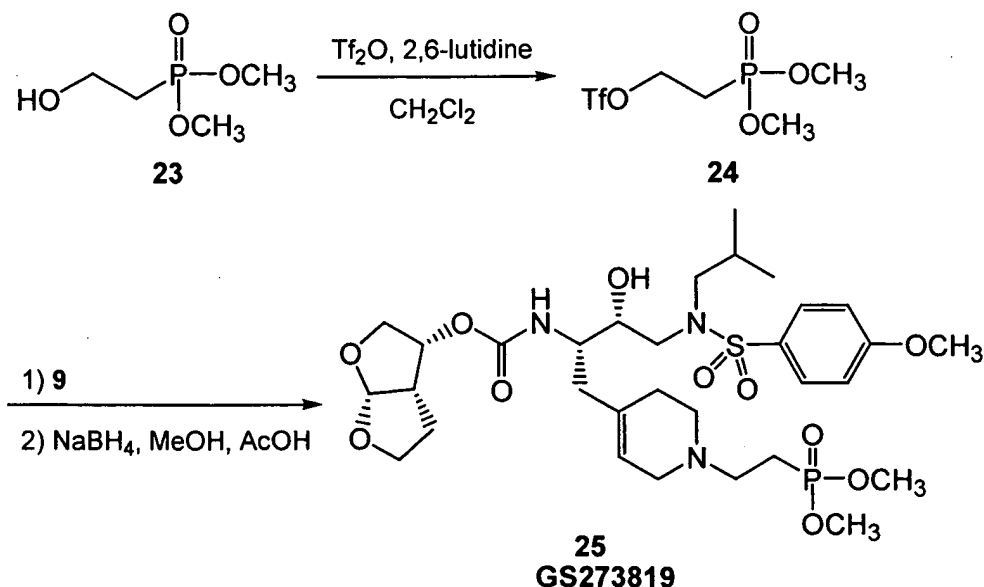
The tetrahydropyridine-prodrug 21: A solution of the pyridine 9 (11.1 mg, 0.020 mmol) and the triflate 20 (11.4 mg, 0.027 mmol) in acetone- $d_6$  (0.67 mL, Aldrich) was stored at room temperature for 7 h and the solution was concentrated under reduced pressure:  $^{31}\text{P}$  NMR (acetone- $d_6$ )  $\delta$  11.7, 10.9; MS (ESI) 838 (M+H). The concentrated crude pyridinium salt was dissolved in ethanol (1 mL) and added 2~3 drops of a solution of acetic acid (0.6 mL, Aldrich) in ethanol (3 mL). The solution was stirred at  $0^\circ\text{C}$  as  $\text{NaBH}_4$  (7~8 mg, Aldrich) was added. More acetic acid solution was added to adjust pH 3~4 of the reaction mixture. Additions of  $\text{NaBH}_4$  and the acetic acid solution were repeated until the reaction was completed. The mixture was carefully concentrated under reduced pressure and the residue was purified by chromatography on C18 reverse phase column material followed by preparative TLC using C18 reverse phase plate to obtain the prodrug 21 (13.6 mg, 70%) as a 2:3 mixture of two diastereomers:  $^1\text{H}$  NMR

(CD<sub>3</sub>CN)  $\delta$  7.78 (d, 2H,  $J$  = 9.0 Hz), 7.48-7.42 (m, 2H), 7.35-7.27 (m, 3H), 7.10 (d, 2H,  $J$  = 9.0 Hz), 5.86 (m, 1H), 5.60 (m, 1H), 5.48 (br, 1H), 5.14-5.03 (m, 2H), 4.29-4.13 (m, 2H), 3.89 (s, 3H), 3.97-3.32 (m, 12H), 3.29 (br, 0.4H), 3.24 (br, 0.6H), 3.02-2.82 (m, 4H), 2.64-2.26 (m, 3H), 2.26-2.08 (m, 1H), 1.94-1.76 (m, 3H), 1.57 (d, 1.8H,  $J$  = 6.9 Hz), 1.46 (d, 1.2H,  $J$  = 6.9 Hz), 1.28 (d, 1.2H,  $J$  = 6.9 Hz), 1.21 (d, 1.8H,  $J$  = 7.2 Hz), 0.92-0.88 (m, 6H); <sup>31</sup>P NMR (CD<sub>3</sub>CN)  $\delta$  14.4 (0.4P), 13.7 (0.6P); MS (ESI) 838 (M+H).

#### Example O16

Metabolite 22: To a solution of the prodrug **21** (10.3 mg, 0.011 mmol) in DMSO (0.1 mL) and acetonitrile (0.2 mL) was added 0.1 M PBS buffer (3 mL) mixed thoroughly to result a suspension. To the suspension was added porcine liver esterase suspension (0.05 mL, EC3.1.1.1, Sigma). After the suspension was stored in 37°C for 1.5 h, the mixture was centrifuged and the supernatant was taken. The product was purified by HPLC and the collected fraction was lyophilized to result the product **22** as trifluoroacetic acid salt (7.9 mg, 86%): <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  7.70 (d, 1H), 7.05 (d, 2H), 5.66 (d, 1H), 5.40 (br, 1H), 5.02 (br, 1H), 4.70 (br, 1H), 3.99-3.89 (m, 2H), 3.81 (s, 3H), 3.83-3.50 (m, 8H), 3.34-2.80 (m, 7H), 2.50-2.18 (m, 3H), 2.03 (m, 1H), 1.92-1.70 (m, 3H), 1.39 (d, 3H), 0.94 (d, 3H), 0.93 (d, 3H); <sup>31</sup>P NMR (D<sub>2</sub>O)  $\delta$  9.0, 8.8; MS (ESI) 734 (M+H).

#### Scheme O5



### Example O17

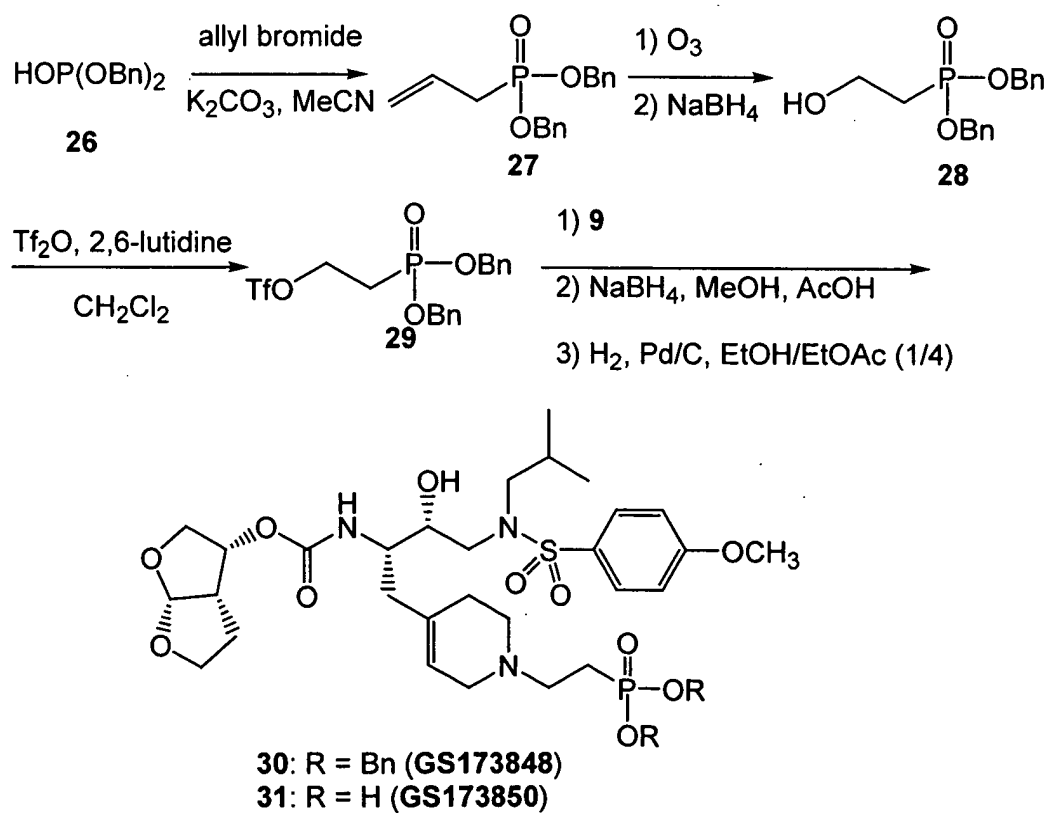
Triflate 24: Triflate **24** was prepared analogously to triflate **20**, except that dimethylhydroxyethylphosphonate **23** (Aldrich) was substituted for ethyl lactate phosphonate with free alcohol **19**.

### Example O18

Tetrahydropyridine **25**: Tetrahydropyridine **25** was prepared analogously to tetrahydropyridine **30**, except that triflate **24** was substituted for triflate **29**.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, 2H), 7.01 (d, 2H), 5.71 (d, 2H), 5.43 (bs, 1H), 5.07-4.87 (m, 1H), 4.16-3.46 (m, 13H), 3.34-3.18 (m, 3H), 3.16-2.80 (m, 5H), 2.52-1.80 (m, 12H), 1.28-1.04 (m, 3H+H<sub>2</sub>O peak), 0.98-0.68 (m, 6H).

### Scheme O6



### Example O19

Dibenzyl phosphonate with double bond **27**: To a stirring solution of allyl bromide (4.15 g, 34 mmol, Aldrich) and dibenzylphosphite (6 g, 23 mmol, Aldrich) in acetonitrile (25 mL) was added potassium carbonate (6.3 g, 46 mmol, powder 325 mesh Aldrich) to create a suspension,

which was heated to 65°C and stirred for 72 hours. The suspension was cooled to room temperature, diluted with ethyl acetate, filtered, and the filtrate was washed with water, then brine, dried (MgSO<sub>4</sub>), concentrated and used directly in the next step.

#### Example O20

Dibenzylhydroxyethylphosphonate 28: Dibenzyl phosphonate with double bond 27 was dissolved in methanol (50mL), chilled to -78°C, stirred, and subjected to ozone by bubbling ozone into the solution for three hours until the solution turned pale blue. The ozone flow was stopped and oxygen bubbling was done for 15 minutes until the solution became colorless. Sodium borohydride (5 g, excess) was added slowly portionwise. After the evolution of gas subsided the solution was allowed to warm to room temperature, concentrated, diluted with ethyl acetate, made acidic with acetic acid and water and partitioned. The ethyl acetate layer was washed with water, then brine and dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel eluting with a gradient of eluent from 50% ethyl acetate in hexane to 100% ethyl acetate, affording 2.76 g of the desired product. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.36 (m, 10H), 5.16-4.95 (m, 4H), 3.94-3.80 (dt, 2H), 2.13-2.01 (dt, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 31.6.

#### Example O21

Dibenzyl phosphonate 30: A solution of the alcohol 28 (53.3 mg, 0.174 mmol) and 2,6-lutidine (0.025 mL, 0.215 mmol, Aldrich) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at -45°C as trifluoromethanesulfonic anhydride (0.029 mL, 0.172 mmol, Aldrich) was added. The solution was stirred for 1 h at -45°C and evaporated under reduced pressure to obtain the crude triflate 29.

A solution of the crude triflate 29, 2,6-lutidine (0.025 mL, 0.215 mmol, Aldrich), and the pyridine 9 in acetone-d<sub>6</sub> (1.5 mL, Aldrich) was stored at room temperature for 2 h. The solution was concentrated under reduced pressure to obtain crude pyridinium product: <sup>31</sup>P NMR (acetone-d<sub>6</sub>) δ 25.8; MS (ESI) 852 (M<sup>+</sup>).

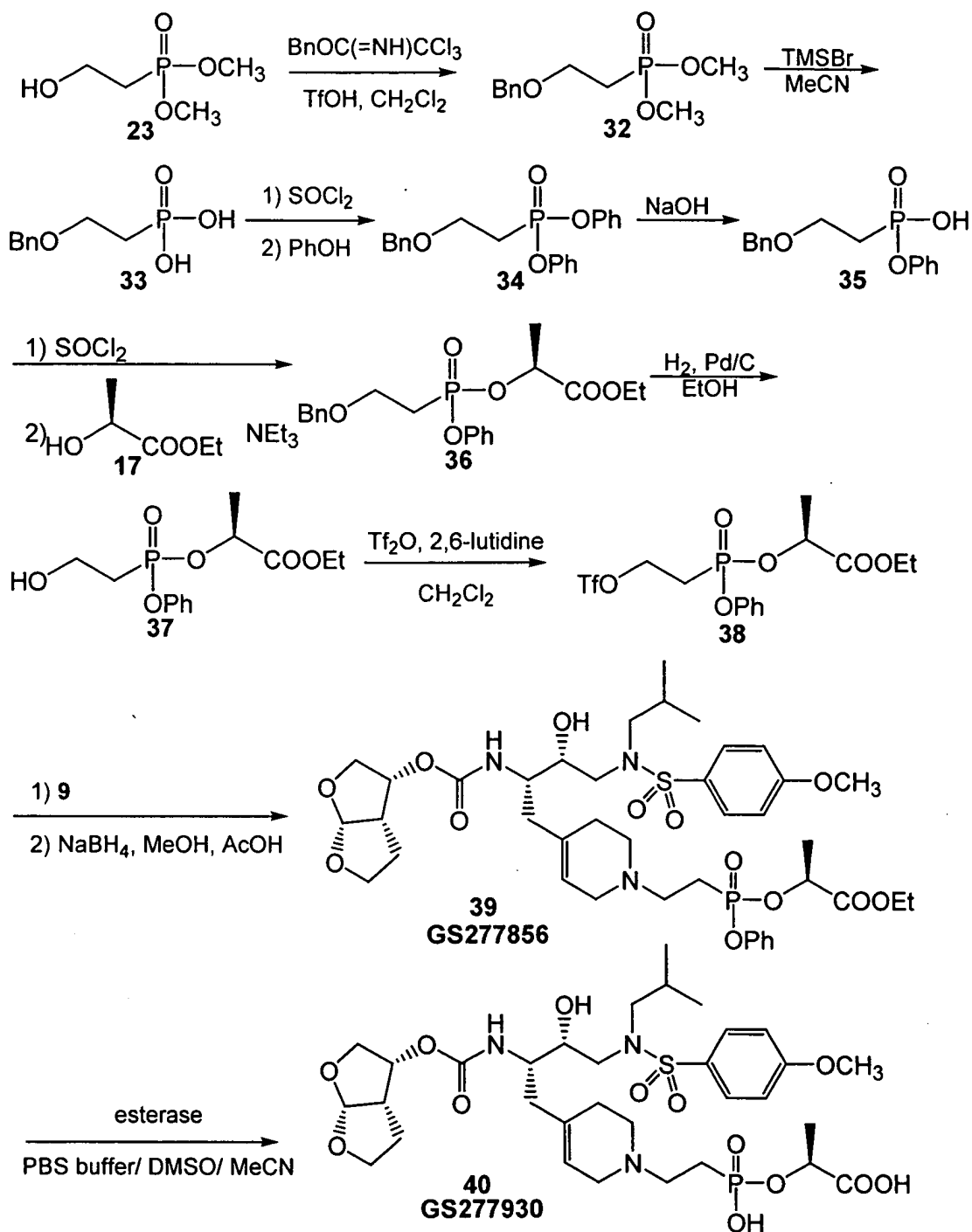
To a solution of the crude pyridinium salt in ethanol (2 mL) was added 7~8 drops of a solution of acetic acid (0.4 mL, Aldrich) in ethanol (2 mL). The solution was stirred at 0°C as NaBH<sub>4</sub> (7~8 mg) was added. The solution was maintained to be pH 3-4 by adding the acetic acid solution. More NaBH<sub>4</sub> and the acetic acid were added until the reduction was completed. After 4 h, the mixture was concentrated and the remaining residue was dissolved in saturated

NaHCO<sub>3</sub> (10 mL). The product was extracted with EtOAc (10 mL x 3), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by repeated chromatography on silica gel followed by HPLC purification. Lyophilization of the collected fraction resulted the product **30** (13.5 mg, 26%) as trifluoroacetic acid salt: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, 2H, *J* = 8.7 Hz), 7.36 (br, 10H), 7.00 (d, 2H, *J* = 8.7 Hz), 5.69 (d, 1H, *J* = 5.1 Hz), 5.41 (br, 1H), 5.13-4.93 (m, 6H), 4.05-2.5 (m, 19H), 3.88 (s, 3H), 2.5-1.9 (m, 5H), 1.90-1.74 (m, 2H), 0.88 (d, 6H, *J* = 6.1 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 25.8; MS (ESI) 856 (M+H).

#### Example O22

Phosphonic acid **31**: A mixture of the dibenzyl phosphonate **30** (9.0 mg, 0.009 mmol) and 10% Pd/C (5.2 mg, Aldrich) in EtOAc (2 mL) and ethanol (0.5 mL) was stirred under H<sub>2</sub> atmosphere for 3 h at room temperature. After the mixture was filtered through celite, a drop of trifluoroacetic acid (Aldrich) was added to the filtrate and the filtrate was concentrated to dryness to afford the product **31** (6.3 mg, 86%): <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.76 (d, 2H, *J* = 9.0 Hz), 7.11 (d, 2H, *J* = 9.0 Hz), 5.69 (d, 1H, *J* = 5.1 Hz), 5.54 (br, 1H), 5.09 (br, 1H), 4.05-3.84 (m, 4H), 3.89 (s, 3H), 3.84-3.38 (m, 9H), 3.07 (dd, 2H, *J* = 13.5 and 8.4 Hz), 2.9-2.31 (m, 5H), 2.31-1.83 (m, 6H), 0.92 (d, 3H, *J* = 6.3 Hz), 0.85 (d, 3H, *J* = 6.9 Hz); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 21.6; MS (ESI) 676 (M+H).

## Scheme O7



## Example O23

**Benzylether 32:** A solution of dimethyl hydroxyethylphosphonate (5.0 g, 32.5 mmol, Across) and benzyl 2,2,2-trichloroacetimidate (97.24 mL, 39.0 mmol, Aldrich) in  $\text{CH}_2\text{Cl}_2$  (100

mL) at 0°C under a nitrogen atmosphere was treated with trifluoromethanesulfonic acid (0.40 mL). Stirring was performed for three hours at 0°C and the reaction was then allowed to warm to room temperature while stirring continued. The reaction continued for 15 hours, and the reaction mixture was then diluted with dichloromethane, washed with saturated sodium bicarbonate, washed with brine, dried (MgSO<sub>4</sub>), concentrated under reduced pressure and chromatographed on silica gel eluting with a gradient of eluent from 60% EtOAc in hexane to 100% EtOAc to afford 4.5 g, (57%) of the benzyl ether as a colorless liquid. <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 31.5.

#### Example O24

Diacid 33: A solution of benzylether 32 (4.5 g, 18.4 mmol) was dissolved in anhydrous acetonitrile (100mL), chilled to 0°C under a nitrogen atmosphere and treated with TMS bromide (9.73 mL, 74mmol). The reaction mixture was warmed to room temperature and after 15 hours of stirring was concentrated repeatedly with MeOH/water to afford the diacid, which was used directly in the next step. <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 31.9.

#### Example O25

Diphenylphosphonate 34 : Diacid 33 (6.0 g, 27 mmol) was dissolved in toluene and concentrated under reduced pressure three times, dissolved in anhydrous acetonitrile, stirred under a nitrogen atmosphere, and treated with thionyl chloride (20 mL, 270 mmol) by slow addition. The solution was heated to 70°C for two hours, then cooled to room temperature, concentrated and dissolved in anhydrous dichloromethane, chilled to -78°C and treated with phenol (15 g, 162 mmol) and triethylamine (37 mL, 270 mmol). The reaction mixture was warmed to room temperature and stirred for 15 hours, and was then diluted with ice cold dichloromethane, washed with ice cold 1 N. NaOH, washed with ice cold water, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The resulting residue was used directly in the next step. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40-7.16 (d, 15H), 4.55 (s, 2H), 3.98-3.84 (m, 2H), 2.55-2.41 (m, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 22.1.

#### Example O26

Mono acid 35: Monoacid 35 was prepared using conditions analogous to those used to prepare monoacid 16, except that diphenylphosphonate 34 was substituted for benzylether 15. <sup>1</sup>H

NMR (CDCl<sub>3</sub>)  $\delta$  7.38-7.16 (d, 10H), 4.55 (s, 2H), 3.82-3.60 (m, 3H), 2.33-2.21 (m, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  29.0.

#### Example O27

Ethyl lactate phosphonate 36: Ethyl lactate phosphonate 36 was prepared analogously to ethyl lactate phosphonate 18 except monoacid 35 was substituted for monoacid 16. <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  27.0, 25.6.

#### Example O28

Ethyl lactate phosphonate with free alcohol 37: Ethyl lactate phosphonate with free alcohol 37 was prepared analogously to ethyl lactate phosphonate with free alcohol 19 except that ethyl lactate phosphonate 36 was substituted for ethyl lactate phosphonate 18. <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  28.9, 26.8.

#### Example O29

Triflate 38: A solution of the alcohol 37 (663 mg, 2.19 mmol) and 2,6-lutidine (0.385 mL, 3.31 mmol, Aldrich) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred at -45°C as trifluoromethanesulfonic anhydride (0.48 mL, 2.85 mmol, Aldrich) was added. The solution was stirred for 1.5 h at -45°C, diluted with ice-cold water (50 mL), and extracted with EtOAc (30 mL x 2). The combined extracts were washed with ice cold water (50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to obtain a crude mixture of two diastereomers (910 mg, 96%, 1:3 ratio): <sup>1</sup>H NMR (acetone-d<sub>6</sub>)  $\delta$  7.48-7.37 (m, 2H), 7.37-7.18 (m, 3H), 5.2-4.95 (m, 3H), 4.3-4.02 (m, 2H), 3.38-3.0 (m, 1H), 3.0-2.7 (m, 2H), 2.1-1.9 (m, 1H), 1.52 (d, 1H), 1.4 (d, 2H), 1.4-1.1 (m, 3H); <sup>31</sup>P NMR (acetone-d<sub>6</sub>)  $\delta$  21.8 (0.75P), 20.5 (0.25P).

#### Example O30

The prodrug 39: A solution of the crude triflate 38 (499 mg, 1.15 mmol) and the pyridine 9 (494 mg, 0.877 mmol) in acetone (5 mL) was stirred at room temperature for 16.5 h. The solution was concentrated under reduced pressure to obtain the crude pyridinium salt.

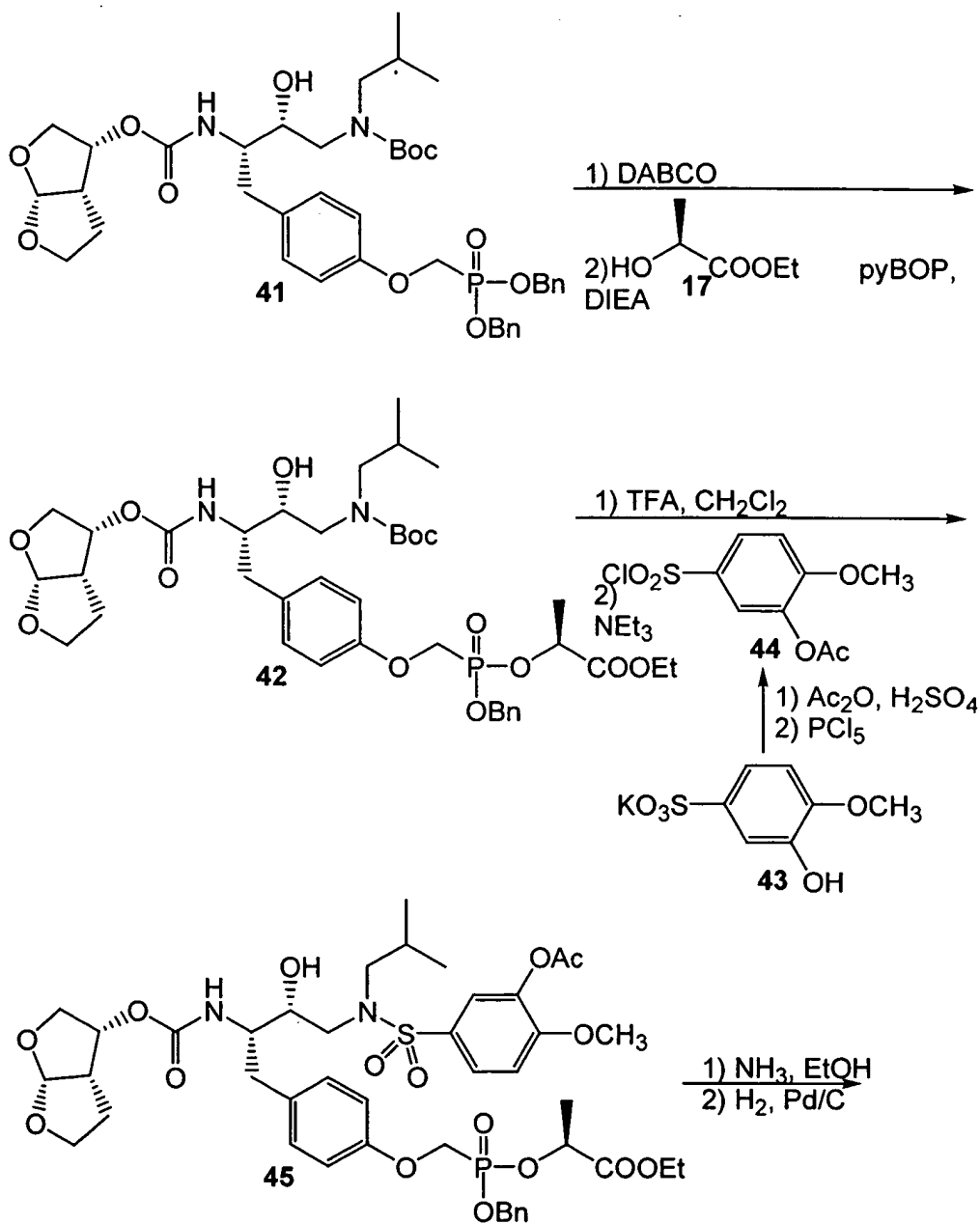
To a solution of the crude pyridinium salt in ethanol (10 mL) was added 5 drops of a solution of acetic acid (1 mL) in ethanol (5 mL). The solution was stirred at 0°C as NaBH<sub>4</sub> (~10 mg, Aldrich) was added. The solution was maintained to be pH 3-4 by adding the acetic acid

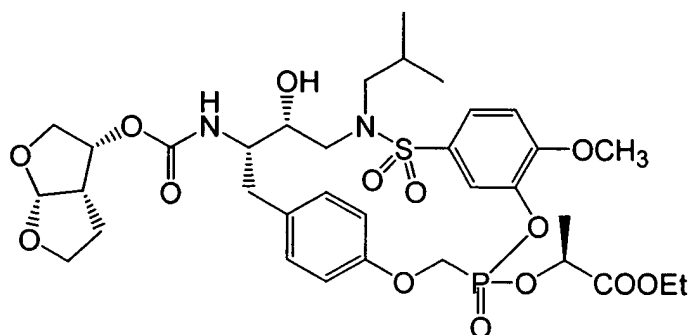
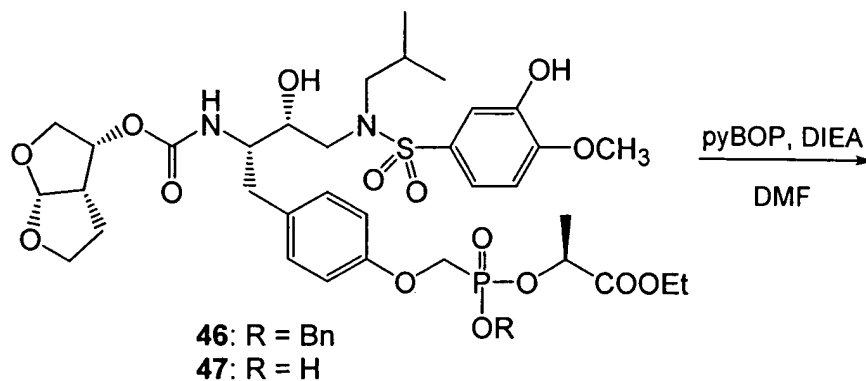
solution. More NaBH<sub>4</sub> and the acetic acid were added until the reduction was completed. After 5.5 h, the mixture was concentrated under reduced pressure and the remaining residue was dissolved in ice-cold saturated NaHCO<sub>3</sub> (50 mL). The product was extracted with ice-cold EtOAc (30 mL x 2) and the combined extracts were washed with 50% saturated NaHCO<sub>3</sub> (50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by a chromatography on silica gel followed by a chromatography on C18 reverse phase column material. Lyophilization of the collected fraction resulted the product **39** mixture (376 mg, 50%, ~2.5:1 ratio) as trifluoroacetic acid salt: <sup>1</sup>H NMR (CD<sub>3</sub>CN+TFA) δ 7.78 (d, 2H, *J* = 8.7 Hz), 7.52-7.42 (m, 2H); 7.37-7.22 (m 3H), 7.10 (d, 2H, *J* = 8.7 Hz), 5.78 (d, 1H, *J* = 9.0 Hz), 5.64 (m, 1H), 5.50 (br, 1H), 5.08 (m, 2H), 4.31-4.12 (m, 2H), 4.04-3.42 (m, 11H), 3.90 (s, 3H), 3.29 (m, 2H), 3.23 -3.16 (m, 1H), 3.08-2.78 (m, 6H), 2.76-2.27 (m, 5H), 2.23-2.11 (m, 1H), 2.08-1.77 (m, 3H), 1.58 (d, 0.9H, *J* = 7.2 Hz), 1.45 (d, 2.1H, *J* = 6.6 Hz), 1.32-1.20 (m, 3H), 0.95 - 0.84 (m, 6H); <sup>31</sup>P NMR (CD<sub>3</sub>CN+TFA) δ 24.1 and 23.8, 22.2 and 22.1; MS (ESI) 852 (M+H).

#### Example O31

Metabolite 40: To a solution of the prodrug **39** (35.4 mg, 0.037 mmol) in DMSO (0.35 mL) and acetonitrile (0.70 mL) was added 0.1 M PBS buffer (10.5 mL) mixed thoroughly to result a suspension. To the suspension was added porcine liver esterase suspension (0.175 mL, EC3.1.1.1, Sigma). After the suspension was stored in 37°C for 6.5 h, the mixture was filtered through 0.45 μm membrane filter and the filtrate was purified by HPLC. The collected fraction was lyophilized to result the product **40** as trifluoroacetic acid salt (28.8 mg, 90%): <sup>1</sup>H NMR (D<sub>2</sub>O) δ 7.96 (d, 2H, *J* = 8.7 Hz), 7.32 (d, 2H, *J* = 8.7 Hz), 5.89 (d, 1H, *J* = 5.1 Hz), 5.66 (br, 1H), 5.27 (m, 1H), 4.97 (m, 1H), 4.23-4.12 (m, 2H), 4.08 (s, 3H), 4.06-3.10 (m, 14H), 3.03 (dd, 1H, *J* = 14.1 and 6.6 Hz), 2.78-1.97 (m, 9H), 1.66 (d, 3H, *J* = 6.9 Hz), 1.03 (d, 3H, *J* = 7.5 Hz), 1.01 (d, 3H, *J* = 6.9 Hz); <sup>31</sup>P NMR (CD<sub>3</sub>CN+TFA) δ 20.0, 19.8; MS (ESI) 748 (M+H).

**Scheme O8**





48A: a minor diastereomer (GS277932)

48B: a major diastereomer (GS277933)

### Example O32

Compound 42: The dibenzyl phosphonate **41** (947 mg, 1.21 mmol) was treated with DABCO (140.9 mg, 1.26 mmol, Aldrich) in 4.5 mL toluene to obtain the monoacid (890 mg, 106%). The crude monoacid (890 mg) was dried by evaporation with toluene twice and dissolved in DMF (5.3 mL) with ethyl (*S*)-lactate (0.3 mL, 2.65 mmol, Aldrich) and pyBOP (945 mg, 1.82 mmol, Aldrich) at room temperature. After diisopropylethylamine (0.85 mL, 4.88 mmol, Aldrich) was added, the solution was stirred at room temperature for 4 h and concentrated under reduced pressure to a half volume. The resulting solution was diluted with 5% aqueous HCl (30 mL) and the product was extracted with EtOAc (30 mL x 3). After the combined extracts were dried (MgSO<sub>4</sub>) and concentrated, the residue was chromatographed on silica gel to afford the compound **42** (686 mg, 72%) as a mixture of two diastereomers (2:3 ratio): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.46-7.32 (m, 5H), 7.13 (d, 2H, *J* = 8.1 Hz), 6.85 (t, 2H, *J* = 8.1 Hz), 5.65 (m, 1H), 5.35-4.98 (m, 4H), 4.39 (d, 0.8H, *J* = 10.2 Hz), 4.30-4.14 (m, 3.2H), 3.98 (dd, 1H, *J* = 9.3 and 6.0 Hz), 3.92-3.78 (m, 3H), 3.78-3.55 (m, 3H), 3.16-2.68 (m, 6H), 1.85 (m, 1H), 1.74-1.55 (m, 2H), 1.56 (d, 1.8H, *J* = 7.2 Hz), 1.49 (d, 1.2H), 1.48 (s, 9H), 1.30-1.23 (m, 3H), 0.88 (d, 3H, *J* = 6.3

Hz), 0.87 (d, 3H,  $J = 6.3$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.8 (0.4P), 19.5 (0.6P); MS (ESI) 793 (M+H).

#### Example O33

Compound 45: A solution of compound **42** (101 mg, 0.127 mmol) and trifluoroacetic acid (0.27 mL, 3.5 mmol, Aldrich) in  $\text{CH}_2\text{Cl}_2$  (0.6 mL) was stirred at  $0^\circ\text{C}$  for 3.5 h and concentrated under reduced pressure. The resulting residue was dried in vacuum to result the crude amine as TFA salt.

A solution of the crude amine salt and triethylamine (0.072 mL, 0.52 mmol, Aldrich) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was stirred at  $0^\circ\text{C}$  as the sulfonyl chloride **42** (37 mg, 0.14 mmol) was added. After the solution was stirred at  $0^\circ\text{C}$  for 4 h and 0.5 h at room temperature, the reaction mixture was diluted with saturated  $\text{NaHCO}_3$  (20 mL) and extracted with EtOAc (20 mL x 1; 15 mL x 2). The combined organic fractions were washed with saturated NaCl solution, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. Purification by chromatography on silica gel provided the sulfonamide **45** (85 mg, 72%) as a mixture of two diastereomers (~1:2 ratio):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45-7.31 (m, 7H), 7.19 (d, 1H,  $J = 8.4$  Hz), 7.12 (d, 2H,  $J = 7.8$  Hz), 6.85 (m, 2H), 5.65 (d, 1H,  $J = 5.4$  Hz), 5.34-5.16 (m, 2H), 5.13-4.97 (m, 2H), 4.97-4.86 (m, 1H), 4.38 (d, 0.7H,  $J = 10.8$  Hz), 4.29-4.12 (m, 3.3H), 3.96 (dd, 1H,  $J = 9.3$  and  $6.3$  Hz), 3.89 (s, 3H), 3.92-3.76 (m, 3H), 3.76-3.64 (m, 2H), 3.64-3.56 (br, 1H), 3.34-3.13 (m, 1H), 3.11-2.70 (m, 6H), 2.34 (s, 3H), 1.86 (m, 1H,  $J = 7.0$  Hz), 1.75-1.58 (m, 2H), 1.56 (d, 2H,  $J = 7.2$  Hz), 1.49 (d, 1H,  $J = 7.2$  Hz), 1.29-1.22 (m, 3H), 0.94 (d, 3H,  $J = 6.6$  Hz), 0.90 (d, 3H,  $J = 6.9$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.7 (0.3P), 19.5 (0.7P); MS (ESI) 921 (M+H).

#### Example O34

Compound 46: Compound **45** (257 mg, 0.279 mmol) was stirred in a saturated solution of ammonia in ethanol (5 mL) at  $0^\circ\text{C}$  for 15 min and the solution was concentrated under reduced pressure. Purification of the residue by chromatography on silica gel provided compound **46** (2.6 mg, 84%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.48-7.34 (m, 4H), 7.22-7.05 (m, 5H), 7.01 (d, 1H,  $J = 8.1$  Hz), 6.87-6.80 (m, 2H), 5.68 (d, 1H,  $J = 4.8$  Hz), 5.32 (dd, 1.3H,  $J = 8.7$  and  $1.8$  Hz), 5.22 (d, 0.7H,  $J = 9.0$  Hz), 5.11-5.00 (m, 3H), 4.47-4.14 (m, 4H), 4.00 (dd, 1H,  $J = 9.9$  and  $6.6$  Hz), 3.93 (s, 3H), 3.95-3.63 (m, 5H), 3.07-2.90 (m, 4H), 2.85-2.75 (m, 1H), 2.75-2.63 (m, 2H), 1.88-1.67 (m, 3H), 1.65-1.55 (m, 2H), 1.57 (d, 2H,  $J = 6.9$  Hz), 1.50 (d, 1H,  $J = 7.2$  Hz),

1.31-1.20 (m, 3H), 0.95 (d, 3H,  $J = 6.6$  Hz), 0.88 (d, 3H,  $J = 6.3$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.7 (0.3P), 19.6 (0.7P); MS (ESI) 879 (M+H).

#### Example O35

Compound 47: A mixture of compound 46 (176 mg, 0.200 mmol) and 10% Pd/C (9.8 mg, Aldrich) in EtOAc (4 mL) and ethanol (1 mL) was stirred under  $\text{H}_2$  atmosphere for 3 h at room temperature. After the mixture was filtered through celite, the filtrate was concentrated to dryness to afford compound 47 (158 mg, 100%) as white powder:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.30-7.16 (m, 2H), 7.12 (d, 2H,  $J = 7.5$  Hz), 7.01 (d, 1H,  $J = 7.8$  Hz), 6.84 (d, 2H,  $J = 7.5$  Hz), 5.66 (d, 1H,  $J = 4.5$  Hz), 5.13-4.97 (m, 2H), 4.38-4.10 (m, 4H), 3.93 (s, 3H), 4.02-3.66 (m, 6H), 3.13-2.69 (m, 7H), 1.96-1.50 (m, 3H), 1.57 (d, 3H,  $J = 6.6$  Hz), 1.26 (t, 3H,  $J = 7.2$  Hz), 0.93 (d, 3H,  $J = 6.0$  Hz), 0.88 (d, 3H,  $J = 6.0$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.1; MS (ESI) 789 (M+H).

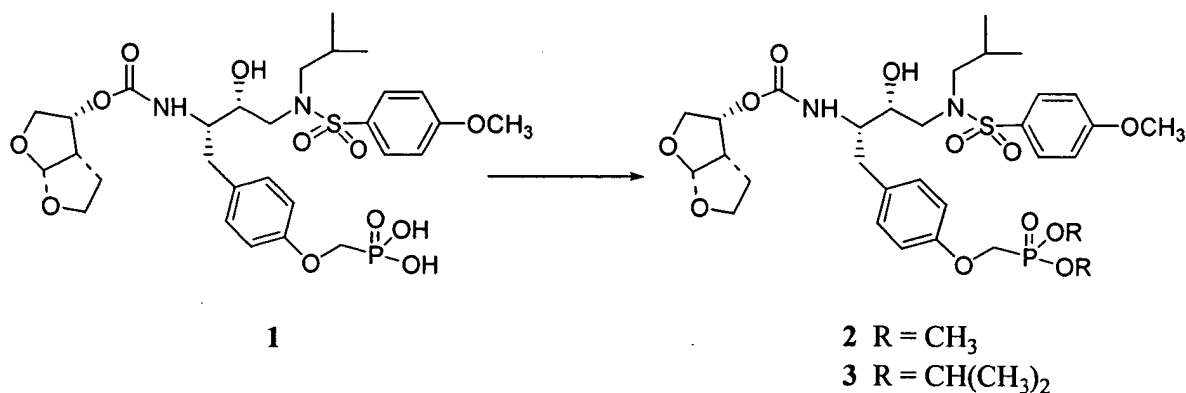
#### Example O36

Compound 48A and 48B: A solution of pyBOP (191 mg, 0.368 mmol, Aldrich) and diisopropylethylamine (0.1 mL, 0.574 mmol, Aldrich) in DMF (35 mL) was stirred at room temperature as a solution of compound 47 (29 mg, 0.036 mmol) in DMF (5.5 mL) was added over 16 h. After addition, the solution was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was dissolved in ice-cold water and extracted with EtOAc (20 mL x 1; 10 mL x 2). The combined extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel followed by preparative TLC gave two isomers of structure 48 (1.0 mg, 3.6% and 3.6 mg, 13%). Isomer 48A:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.39 (m, 1H), 7.12 (br, 1H), 7.01 (d, 2H,  $J = 8.1$  Hz), 6.98 (br, 1H), 6.60 (d, 2H,  $J = 8.1$  Hz), 5.75 (d, 1H,  $J = 5.1$  Hz), 5.37-5.28 (m, 2H), 5.18 (q, 1H,  $J = 8.7$  Hz), 4.71 (dd, 1H,  $J = 14.1$  and 7.5 Hz), 4.29 (m, 3H), 4.15-4.06 (m, 1H), 3.99 (s, 3H), 4.05-3.6 (m, 5H), 3.35 (m, 1H), 3.09 (br, 1H), 2.90-2.78 (m, 3H), 2.2-2.0 (m, 3H), 1.71 (d, 3H,  $J = 6.6$  Hz), 1.34 (t, 3H,  $J = 6.9$  Hz), 1.01 (d, 3H,  $J = 6.3$  Hz), 0.95 (d, 3H,  $J = 6.3$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.8; MS (ESI) 793 (M+Na); isomer 48B:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.46 (d, 1H,  $J = 9.3$  Hz), 7.24 (br, 1H), 7.00 (d, 2H,  $J = 8.7$  Hz), 6.91 (d, 1H,  $J = 8.7$  Hz), 6.53 (d, 2H,  $J = 8.7$  Hz), 5.74 (d, 1H,  $J = 5.1$  Hz), 5.44 (m, 1H), 5.35 (d, 1H,  $J = 9.0$  Hz), 5.18 (q, 1H,  $J = 7.2$  Hz), 4.68 (dd, 1H,  $J = 14.4$  and 6.3 Hz), 4.23 (m, 3H), 4.10 (m, 1H), 4.04 (s, 3H), 3.77-4.04 (m, 6H), 3.46 (dd, 1H,  $J = 12.9$  and 11.4 Hz), 3.08 (br, 1H), 2.85 (m, 2H), 2.76 (dd, 1H,  $J = 12.9$  and 4.8 Hz), 1.79-2.11 (m, 3H),

1.75 (d, 3H,  $J = 6.6$  Hz), 1.70 (m, 2H), 1.27 (t, 3H,  $J = 6.9$  Hz), 1.01 (d, 3H,  $J = 6.6$  Hz), 0.93 (d, 3H,  $J = 6.6$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.4; MS (ESI) 793 ( $\text{M}+\text{Na}$ ).

## Example Section P

### Scheme P1



### Example P1A

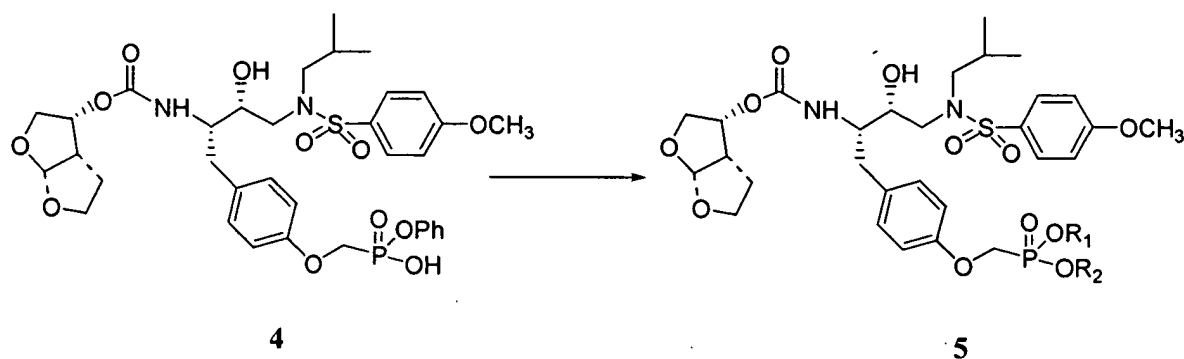
Dimethylphosphonic ester **2** (R = CH<sub>3</sub>): To a flask was charged with phosphonic acid **1** (67 mg, 0.1 mmol), methanol (0.1 mL, 2.5 mmol) and 1, 3-dicyclohexylcarbodiimide (83 mg, 0.4 mmol), then pyridine (1 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH<sub>2</sub>Cl<sub>2</sub>, 1% to 7%) to give **2** (39 mg, 56 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71(d,  $J = 8.7$  Hz, 2H), 7.15 (d,  $J = 8.7\text{Hz}$ , 2H), 7.00 (d,  $J = 8.7$  Hz, 2H), 6.87 (d,  $J = 8.7$  Hz, 2H), 5.65 (d,  $J = 5.1$  Hz, 1H), 5.10-4.92 (m, 4H), 4.26 (d,  $J = 9.9$  Hz, 2H), 3.96 -3.65 (m overlapping s, 15H), 3.14-2.76 (m, 7H), 1.81-1.55 (m, 3H), 0.91 (d,  $J = 6.6$  Hz, 3H), 0.88 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.7; MS (ESI) 723 ( $\text{M}+\text{Na}$ ).

### Example P1B

Diisopropylphosphonic ester **3** (R = CH (CH<sub>3</sub>)<sub>2</sub>) was synthesized in the same manner in 60% yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71(d,  $J = 8.7$  Hz, 2H), 7.15 (d,  $J = 8.7\text{Hz}$ , 2H), 7.15 (d,  $J = 8.7$

Hz, 2H), 6.99 (d,  $J = 8.7$  Hz, 2H), 6.87 (d,  $J = 8.7$  Hz, 2H), 5.66 (d,  $J = 5.1$  Hz, 1H), 5.08-4.92 (m, 3H), 4.16 (d,  $J = 10.5$  Hz, 2H), 3.98 -3.68 (m overlapping s, 9H), 3.16-2.78 (m, 7H), 1.82-1.56 (m, 3H), 1.37 (t,  $J = 6.3$  Hz, 6H), 0.93 (d,  $J = 6.6$  Hz, 3H), 0.88 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3; MS (ESI) 779 ( $\text{M}+\text{Na}$ ).

#### Scheme P2



Compound	R <sub>1</sub>	R <sub>2</sub>
5a	OPh	mix-Hba-Et
5b	OPh	( <i>S</i> )-Hba-Et
5c	OPh	( <i>S</i> )-Hba-tBu
5d	OPh	( <i>S</i> )-Hba-EtMor
5e	OPh	( <i>R</i> )-Hba-Et

#### Example P2A

Monolactate **5a** ( $\text{R}_1 = \text{OPh}$ ,  $\text{R}_2 = \text{Hba-Et}$ ): To a flask was charged with monophenyl phosphonate **4** (250 mg, 0.33 mmol), 2-hydroxy-*n*-butyric acid ethyl ester (145 mg, 1.1 mmol) and 1, 3-dicyclohexylcarbodiimide (226 mg, 1.1 mmol), then pyridine (2.5 mL) was added under  $\text{N}_2$ . The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with  $\text{NH}_4\text{Cl}$ , brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel ( $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ , 1:1) to give **5a** (150 mg, 52 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.7$  Hz, 2H), 7.37-7.19 (m, 5H), 7.14 (d,  $J = 8.7$  Hz, 2H), 7.00 (d,  $J = 8.7$  Hz, 2H), 6.91 (d,  $J = 8.7$  Hz, 1H), 6.86 (d,  $J = 8.7$  Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H),

1.81-1.55 (m, 5H), 1.21 (m, 3H), 1.04-0.86 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.5 and 15.1; MS (ESI) 885 (M+Na).

#### Example P2B

Monolactate **5b** (R1 = OPh, R2 = (*S*)-Hba-Et): To a flask was charged with monophenyl phosphonate **4** (600 mg, 0.8 mmol), (*S*)-2-hydroxy-*n*-butyric acid ethyl ester (317 mg, 2.4 mmol) and 1, 3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol), then pyridine (6 mL) was added under  $\text{N}_2$ . The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with  $\text{NH}_4\text{Cl}$ , brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/ $\text{CH}_2\text{Cl}_2$ , 1:1) to give **5b** (360 mg, 52 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J$  = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.15 (d,  $J$  = 8.7 Hz, 2H), 7.00 (d,  $J$  = 8.7 Hz, 2H), 6.92 (d,  $J$  = 8.7 Hz, 1H), 6.86 (d,  $J$  = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.5 and 15.2; MS (ESI) 885 (M+Na).

#### Example P2C

Monolactate **5c** (R1 = OPh, R2 = (*S*)-Hba-*t*Bu): To a flask was charged with monophenyl phosphonate **4** (120 mg, 0.16 mmol), *tert*-butyl (*S*)-2-hydroxybutyrate (77 mg, 0.48 mmol) and 1, 3-dicyclohexylcarbodiimide (99 mg, 0.48 mmol), then pyridine (1 mL) was added under  $\text{N}_2$ . The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with  $\text{NH}_4\text{Cl}$ , brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/ $\text{CH}_2\text{Cl}_2$ , 1:1) to give **5c** (68 mg, 48 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J$  = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.14 (d,  $J$  = 8.7 Hz, 2H), 7.00 (d,  $J$  = 8.7 Hz, 2H), 6.93 (d,  $J$  = 8.7 Hz, 1H), 6.86 (d,  $J$  = 8.7 Hz, 1H), 5.64 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.44 (d,  $J$  = 11 Hz, 9H), 1.04-0.86 (m, 9H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.5 and 15.2; MS (ESI) 913 (M+Na).

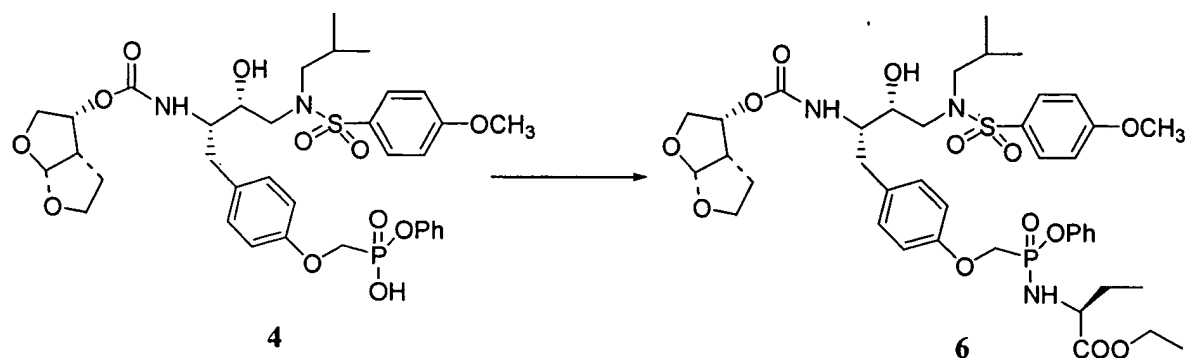
### Example P2D

Monolactate **5d** (R1 = OPh, R2 = (*S*)-Lac-EtMor): To a flask was charged with monophenyl phosphonate **4** (188 mg, 0.25 mmol), (*S*)-lactate ethylmorpholine ester (152 mg, 0.75 mmol) and 1, 3-dicyclohexylcarbodiimide (155 mg, 0.75 mmol), then pyridine (2mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH<sub>2</sub>Cl<sub>2</sub>, 1:9) to give **5d** (98 mg, 42 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.34-7.20 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.21-4.99 (m, 3H), 4.57-4.20 (m, 4H), 3.97 -3.63 (m overlapping s, 13H), 3.01-2.44 (m, 13H), 1.85-1.50 (m, 6H), 0.92 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.4 and 15.3; MS (ESI) 934(M).

### Example P2E

Monolactate **5e** (R1 = OPh, R2 = (*R*)-Hba-Et): To a flask was charged with monophenyl phosphonate **4** (600 mg, 0.8 mmol), (*R*)-2-hydroxy-n-butyric acid ethyl ester (317 mg, 2.4 mmol) and 1, 3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol), then pyridine (6 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 1:1) to give **5e** (345 mg, 50 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.70 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.5 and 15.1; MS (ESI) 885 (M+Na).

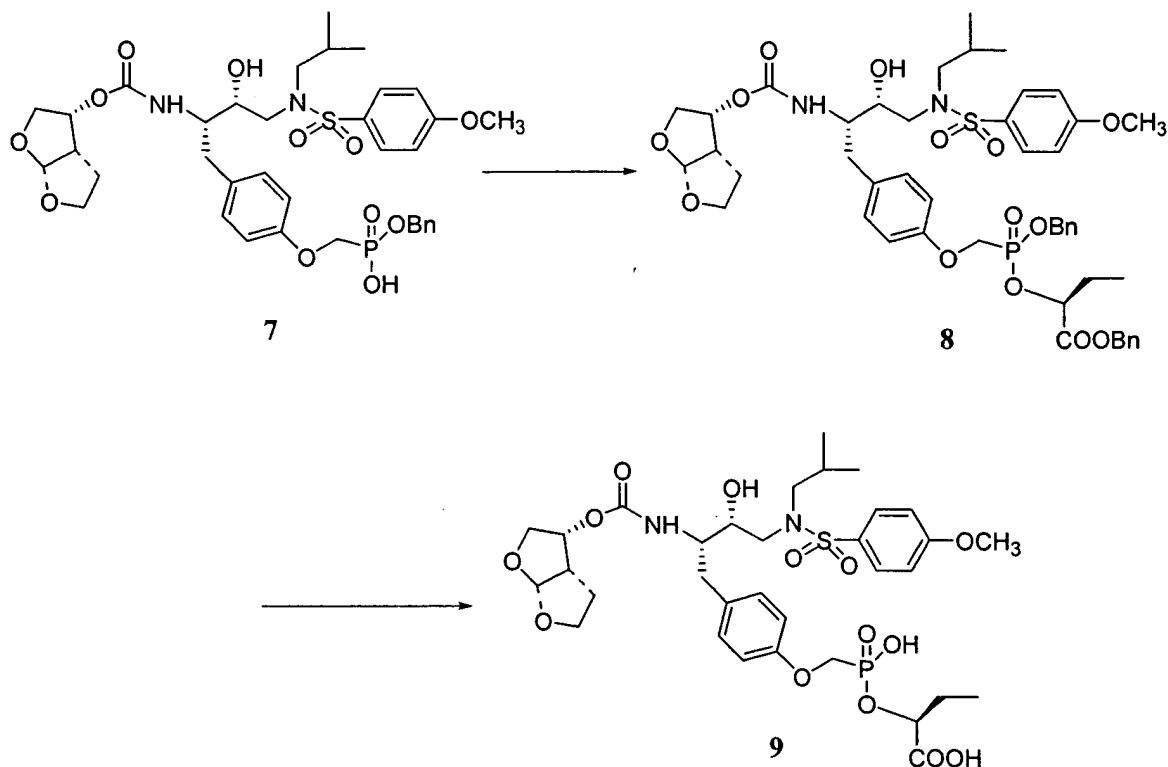
### Scheme P3



### Example P3

**Monoamidate 6:** To a flask was charged with monophenyl phosphonate **4** (120 mg, 0.16 mmol), L-alanine butyric acid ethyl ester hydrochloride (160 mg, 0.94 mmol) and 1, 3-dicyclohexylcarbodiimide (132 mg, 0.64 mmol), then pyridine (1 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH<sub>2</sub>Cl<sub>2</sub>, 1:9) to give **6** (55 mg, 40 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.37-7.23 (m, 5H), 7.16 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.1Hz, 1H), 5.10-4.92 (m, 3H), 4.28 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.7 and 19.6; MS (ESI) 884(M+Na).

#### Scheme P4



#### Example P4A

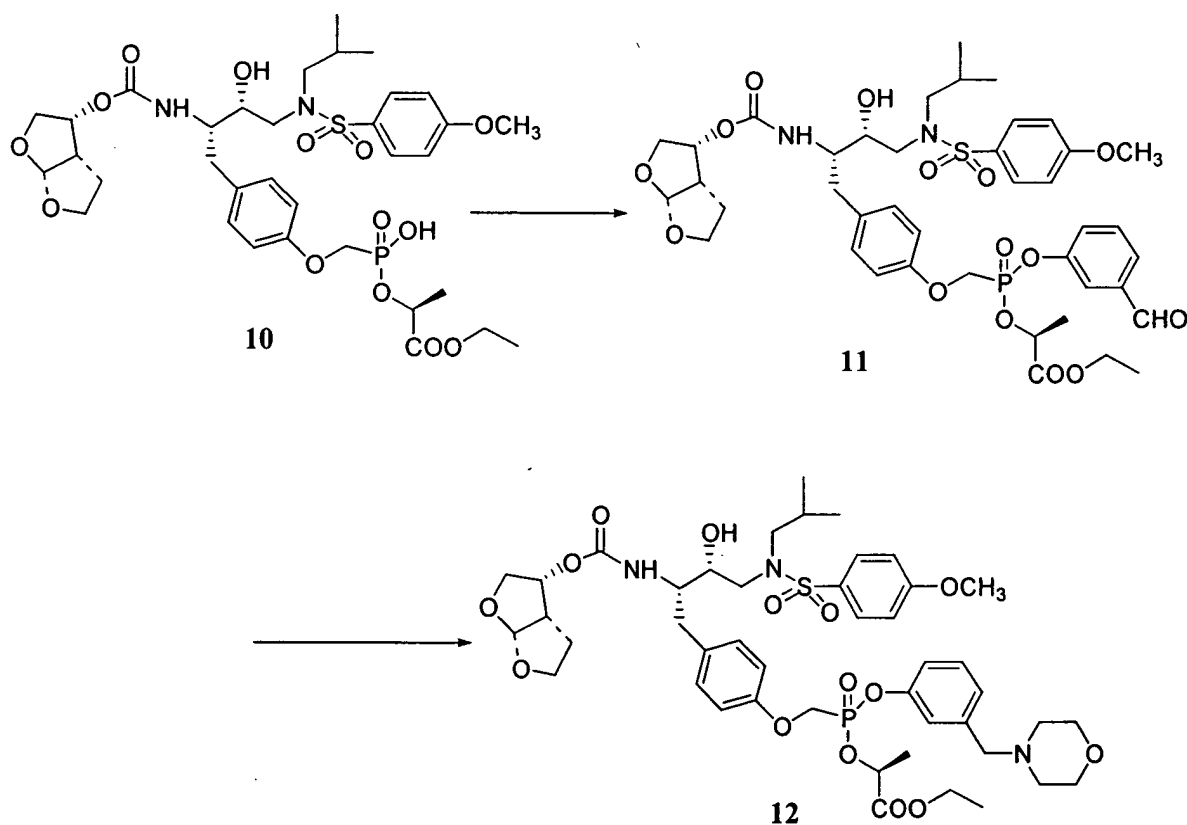
**Compound 8:** To a stirred solution of monobenzyloxymethyl phosphonate **7** (195 mg, 0.26mmol) in 1 mL of DMF at room temperature under N<sub>2</sub> was added benzyl-(s)-lactate (76 mg, 0.39 mmol) and PyBOP (203 mg, 0.39mmol), followed by DIEA (181μL, 1 mmol). After 3 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate/hexane 1:1) to give **8** (120 mg, 50%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, J = 8.7 Hz, 2H), 7.38-7.34 (m, 5H), 7.12 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.24-4.92 (m, 7H), 4.28 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.16-2.76 (m, 7H), 1.95-1.62 (m, 5H), 0.99-0.87 (m, 9H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 21.0 and 19.7; MS (ESI) 962 (M+Na).

#### Example P4B

**Compound 9:** A solution of compound **8** (100 mg) was dissolved in EtOH/ EtOAc (9 mL/ 3mL), treated with 10 % Pd/C (10 mg) and was stirred under H<sub>2</sub> atmosphere (balloon) for 1.5 h. The catalyst was removed by filtration through celite. The filtered was evaporated under

reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the compound **9** (76mg, 94%) as a white solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.76 (d,  $J$  = 8.7 Hz, 2H), 7.18 (d,  $J$  = 8.7 Hz, 2H), 7.08 (d,  $J$  = 8.7 Hz, 2H), 6.90 (d,  $J$  = 8.7 Hz, 2H), 5.59 (d,  $J$  = 5.4 Hz, 1H), 5.03-4.95 (m, 2H), 4.28 (m, 2H), 3.90 -3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 1.96 (m, 3H), 1.61 (m, 2H), 1.18 (m, 3H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.87 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  18.3; MS (ESI) 782 ( $\text{M}+\text{Na}$ ).

#### Scheme P5



#### Example P5A

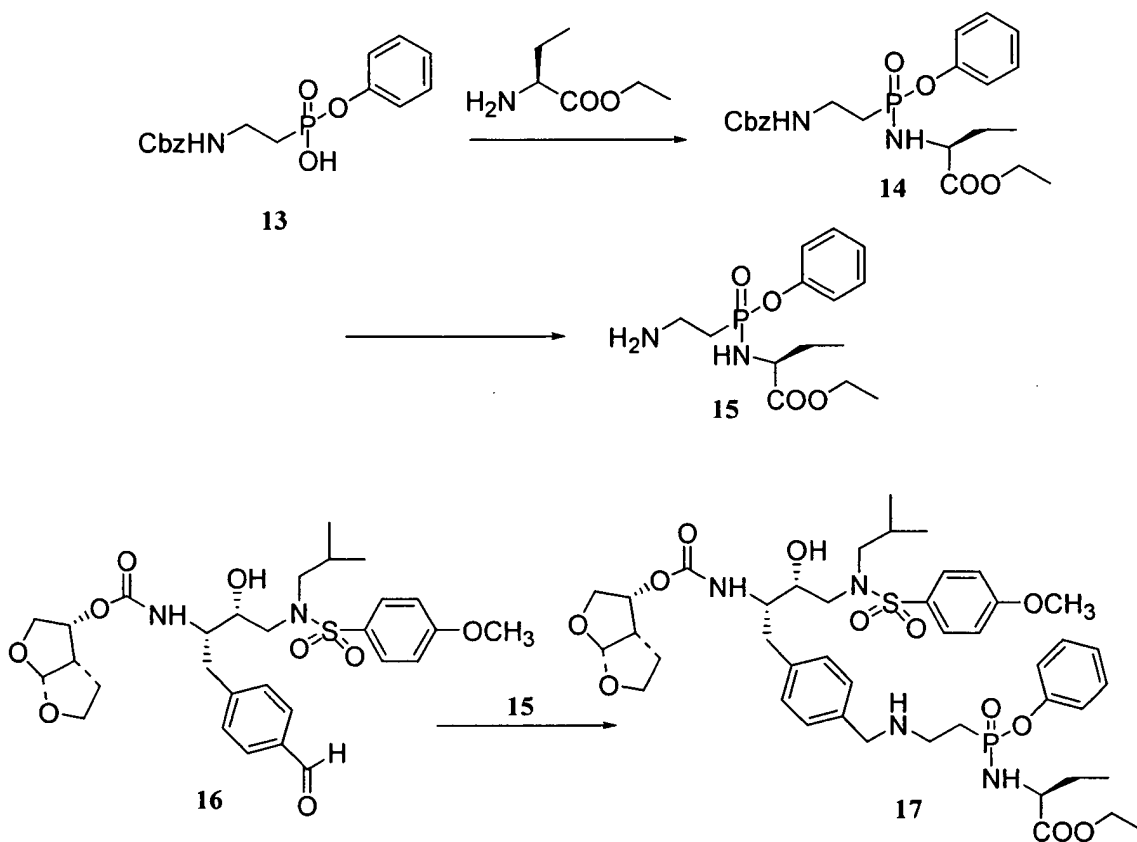
**Compound 11:** To a stirred solution of compound **10** (1 g, 1.3mmol) in 6 mL of DMF at room temperature under  $\text{N}_2$  was added 3-hydroxybenzaldehyde (292 mg, 2.6 mmol) and PyBOP (1 g, 1.95mmol), followed by DIEA (0.9 mL, 5.2 mmol). After 5 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate/hexane 1:1) to give **11** (800 mg, 70%) as a white solid.  $^1\text{H}$  NMR

(CDCl<sub>3</sub>)  $\delta$  9.98 (s, 1H), 7.79-6.88 (m, 12H), 5.65 (m, 1H), 5.21-4.99 (m, 3H), 4.62-4.16 (m, 4H), 3.99 -3.61 (m overlapping s, 9H), 3.11-2.79 (m, 5H), 1.85-1.53 (m, 6H), 1.25 (m, 3H), 0.90 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  17.9 and 15.9; MS (ESI) 899 (M+ Na).

#### Example P5B

**Compound 12:** To a stirred solution of compound **11** (920 mg, 1.05 mmol) in 10 mL of ethyl acetate at room temperature under N<sub>2</sub> was added morpholine (460 mg, 5.25 mmol) and acetic acid (0.25 mL, 4.2 mmol), followed by sodium cyanoborohydride (132 mg, 2.1 mmol). After 20h, the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol / CH<sub>2</sub>Cl<sub>2</sub>, 6%) to give **12** (600 mg, 60%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.71 (d, J = 8.7 Hz, 2H), 7.27 (m, 4H), 7.15 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.89 (m, 2H), 5.65 (m, 1H), 5.21-5.02 (m, 3H), 4.58-4.38 (m, 2H), 4.21-4.16 (m, 2H), 3.99 -3.63 (m overlapping s, 15H), 3.47 (s, 2H), 3.18-2.77 (m, 7H), 2.41 (s, 4H), 1.85-1.53 (m, 6H), 1.25 (m, 3H), 0.90 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  17.4 and 15.2; MS (ESI) 971 (M+Na).

## Scheme P6



### Example P6A

Compound **14**: To a stirred solution of compound **13** (1 g, 3 mmol) in 30 mL of acetonitrile at room temperature under N<sub>2</sub> was added thionyl chloride (0.67 mL, 9 mmol). The resulted mixture was stirred at 60-70°C for 0.5 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 30 mL of DCM, followed by DIEA (1.7 mL, 10 mmol), L-alanine butyric acid ethyl ester hydrochloride (1.7 g, 10 mmol) and TEA (1.7 mL, 12 mmol). After 4h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (Hexane/EtOAc 1:1) to give **14** (670 mg, 50%) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33-7.11 (m, 10H), 5.70 (m, 1H), 5.10 (s, 2H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.76-1.55 (m, 2H), 1.25-1.19 (m, 3H), 0.85-0.71 (m, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 30.2 and 29.9; MS (ESI) 471 (M+Na).

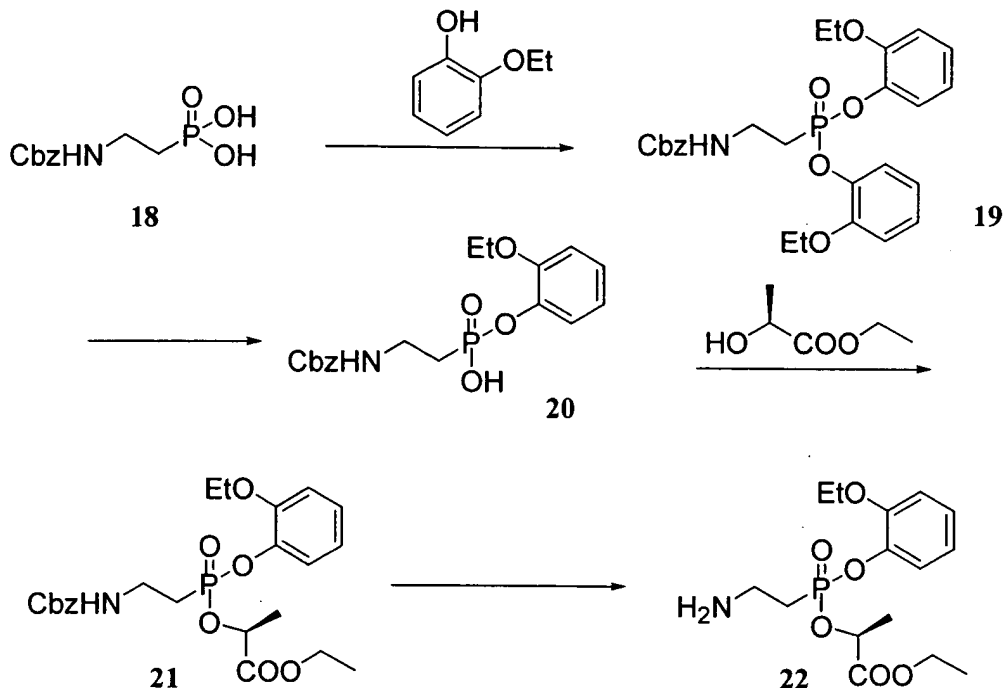
#### Example P6B

Compound **15**: A solution of compound **14** (450mg) was dissolved in 9 mL of EtOH, then 0.15 mL of acetic acid and 10 % Pd/C (90 mg) was added. The resulted mixture was stirred under H<sub>2</sub> atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **15** (300mg, 95%) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.29-7.12 (m, 5H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.70-1.55 (m, 2H), 1.24-1.19 (m, 3H), 0.84-0.73(m, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 29.1 and 28.5; MS (ESI) 315 (M+1).

#### Example P6C

Monoamidate **17**: To a stirred solution of compound **16** (532 mg, 0.9 mmol) in 4 mL of 1,2-dichloroethane was added compound **15** (300 mg, 0.96 mmol) and MgSO<sub>4</sub> (50 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (1.3 mL, 23 mmol) and sodium cyanoborohydride (1.13 g, 18 mmol) were added. The reaction mixture was stirred at room temperature for 1 h under argon. Then aqueous NaHCO<sub>3</sub> (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH / EtOAc, 1/9) to give **17** (600 mg, 60%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (d, J = 8.7 Hz, 2H), 7.33-7.13 (m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.11-4.98 (m, 2H), 4.22 -3.68 (m overlapping s, 15H), 3.20-2.75 (m, 9H), 2.21-2.10 (m, 2H), 1.88-1.55(m, 5H), 1.29-1.19 (m, 3H), 0.94-0.70 (m, 9H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 31.8 and 31.0; MS (ESI) 889 (M).

### Scheme P7



#### Example P7A

**Compound 19:** To a stirred solution of compound **18** (3.7 g, 14.3 mmol) in 70 mL of acetonitrile at room temperature under N<sub>2</sub> was added thionyl chloride (6.3 mL, 86 mmol). The resulted mixture was stirred at 60-70°C for 2 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 150 mL of DCM, followed by TEA (12 mL, 86 mmol) and 2-ethoxyphenol (7.2 mL, 57.2 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate and washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM/EtOAc 9:1) to give **19** (4.2 g, 60%) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32-6.83 (m, 13H), 5.22 (m, 1H), 5.12 (s, 2H), 4.12-3.73 (m, 6H), 2.52-2.42 (m, 2H), 1.41-1.37 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 25.4; MS (ESI) 522 (M+Na).

#### Example P7B

**Compound 20:** A solution of compound **19** (3 g, 6 mmol) was dissolved in 70 mL of acetonitrile at 0°C, then 2N NaOH (12 mL, 24 mmol) was added dropwisely. The reaction

mixture was stirred at room temperature for 1.5 h. Then the solvent was removed under reduced pressure, and the residue diluted with water and extracted with ethyl acetate. The aqueous layer was acidified with conc. HCl to PH = 1, then extracted with ethyl acetate, combined the organic layer and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give compound **20** (2 g, 88%) as a off-white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33-6.79 (m, 9H), 5.10 (s, 2H), 4.12-3.51 (m, 6H), 2.15-2.05 (m, 2H), 1.47-1.33 (m, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 30.5; MS (ESI) 380 (M+1).

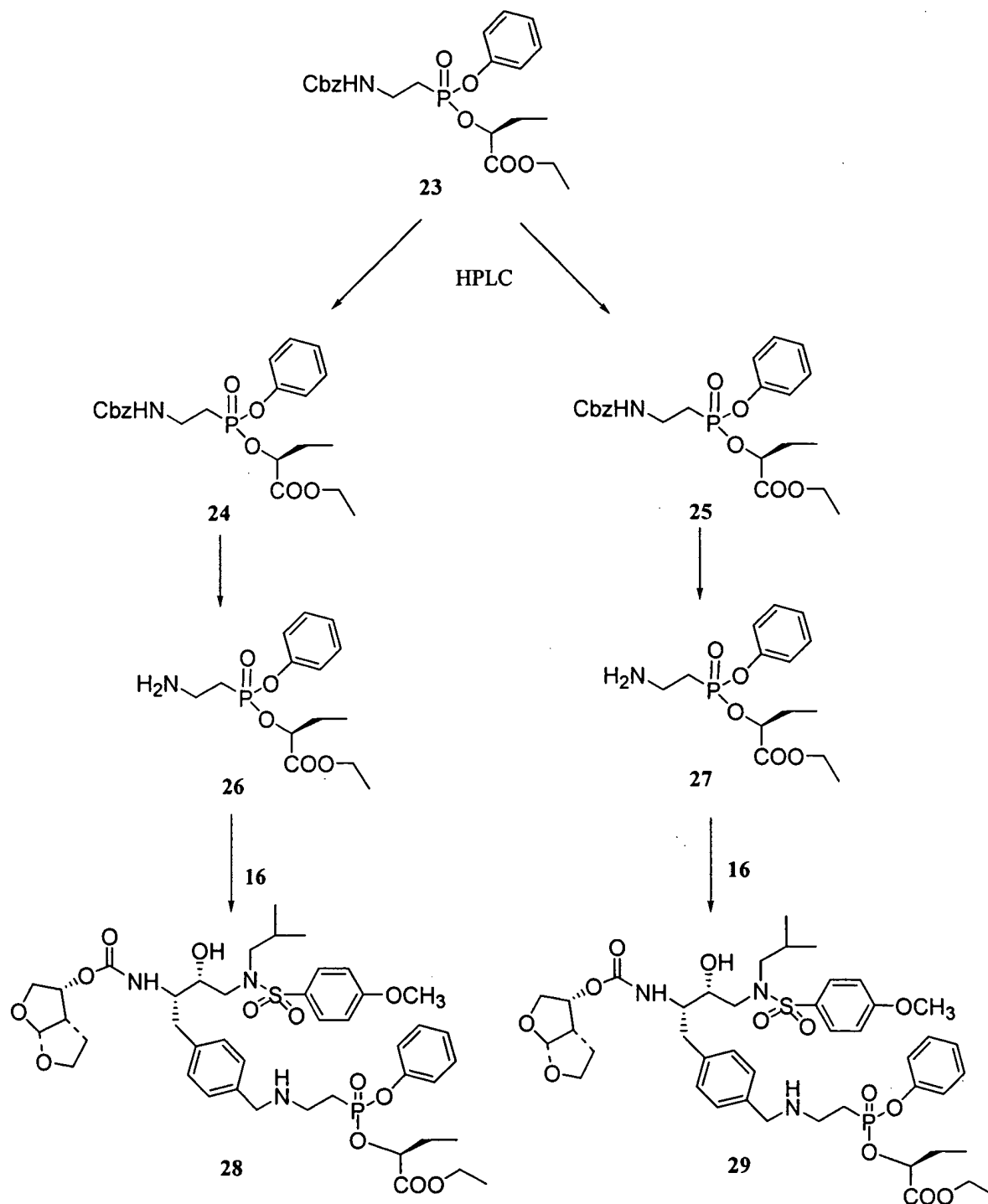
#### Example P7C

Compound **21**: To a stirred solution of compound **20** (1 g, 2.6 mmol) in 20 mL of acetonitrile at room temperature under N<sub>2</sub> was added thionyl chloride (1.1 mL, 15.6 mmol). The resulted mixture was stirred at 60-70°C for 45 min. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 25 mL of DCM, followed by TEA (1.5 mL, 10.4 mmol) and (S) lactate ethyl ester (0.9 mL, 7.8 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM / EtOAc 3:1) to give **21** (370 mg, 30%) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33- 6.84 (m, 9H), 6.17-6.01 (m, 1H), 5.70 (m, 1H), 5.18-5.01 (m, 3H), 4.25-4.04 (m, 4H), 3.78-3.57 (m, 2H), 2.38-2.27 (m, 2H), 1.5-1.23 (m, 9H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 29.2 and 27.3; MS (ESI) 502 (M+Na).

#### Example P7D

Compound **22**: A solution of compound **21** (370mg) was dissolved in 8 mL of EtOH, then 0.12 mL of acetic acid and 10 % Pd/C (72 mg) was added. The resulted mixture was stirred under H<sub>2</sub> atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **22** (320mg, 96%) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.27- 6.86 (m, 4H), 5.98 (s, 2H), 5.18-5.02 (m, 1H), 4.25-4.06 (m, 4H), 3.34-3.24 (m, 2H), 2.44-2.30 (m, 2H), 1.62-1.24 (m, 9H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 28.3 and 26.8; MS (ESI) 346 (M+1).

## Scheme P8



### Example P8A

Compound 24: Compound 23 was purified using a Dynamax SD-200 HPLC system. The mobile phase consisted of acetonitrile: water (65:35, v/v) at a flow rate of 70 mL/ min. The

injection volume was 4 mL. The detection was by fluorescence at 245 nm and peak area ratios were used for quantitations. Retention time was 8.2 min for compound **24** as yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.36-7.19 (m, 10H), 5.88 (m, 1H), 5.12 (s, 2H), 4.90-4.86 (m, 1H), 4.26-4.12 (m, 2H), 3.72-3.61 (m, 2H), 2.36-2.29 (m, 2H), 1.79-1.74 (m, 2H); 1.27 (t,  $J = 7.2$  Hz, 3H), 0.82 (t,  $J = 7.2$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.3; MS (ESI) 472 ( $\text{M}+\text{Na}$ ).

#### Example P8B

Compound **25** was purified in the same manner and retention time was 7.9 min for compound **25** as yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.34-7.14 (m, 10H), 5.75 (m, 1H), 5.10 (s, 2H), 4.96-4.91 (m, 1H), 4.18-4.12 (m, 2H), 3.66-3.55 (m, 2H), 2.29-2.19 (m, 2H), 1.97-1.89 (m, 2H); 1.21 (t,  $J = 7.2$  Hz, 3H), 0.97 (t,  $J = 7.2$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.2; MS (ESI) 472 ( $\text{M}+\text{Na}$ ).

#### Example P8C

Compound **26**: A solution of compound **24** (1 g) was dissolved in 20 mL of EtOH, then 0.3 mL of acetic acid and 10 % Pd/C (200 mg) was added. The resulted mixture was stirred under  $\text{H}_2$  atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **26** (830mg, 99 %) as a colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.46-7.19 (m, 5H), 4.92-4.81 (m, 1H), 4.24-4.21 (m, 2H), 3.41-3.28 (m, 2H), 2.54-2.38 (m, 2H), 1.79-1.74 (m, 2H), 1.27 (t,  $J = 7.2$  Hz, 3H), 0.80 (t,  $J = 7.2$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.9; MS (ESI) 316 ( $\text{M}+1$ ).

#### Example P8D

Compound **27**: A solution of compound **25** (700g) was dissolved in 14 mL of EtOH, then 0.21 mL of acetic acid and 10 % Pd/C (140 mg) was added. The resulted mixture was stirred under  $\text{H}_2$  atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **27** (510mg, 98 %) as a colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.39-7.18 (m, 5H), 4.98-4.85 (m, 1H), 4.25-4.22 (m, 2H), 3.43-3.28 (m, 2H), 2.59-2.41 (m, 2H), 1.99-1.85 (m, 2H), 1.28 (t,  $J = 7.2$  Hz, 3H), 1.02 (t,  $J = 7.2$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.2; MS (ESI) 316 ( $\text{M}+1$ ).

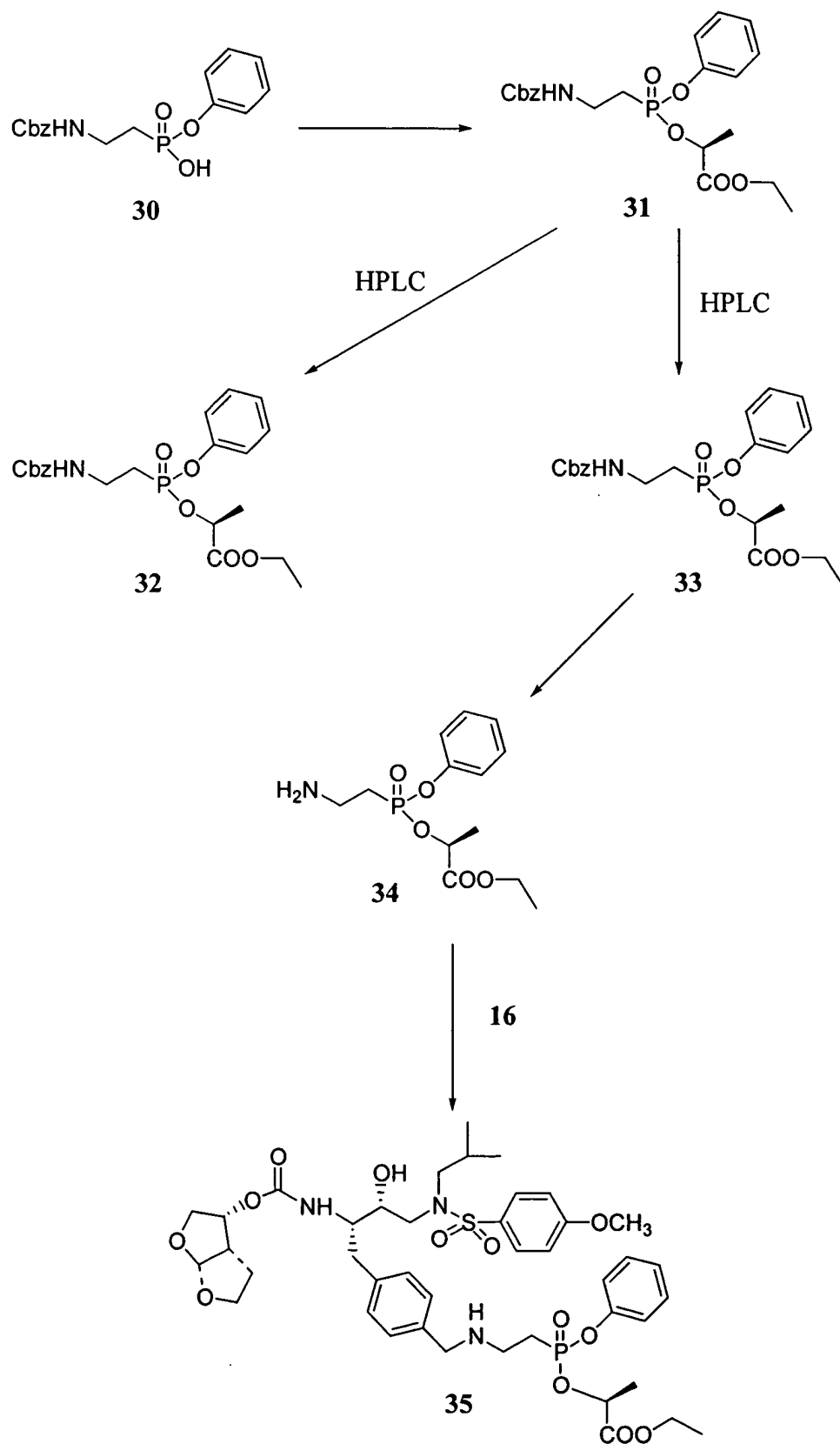
#### Example P8E

Compound **28**: To a stirred solution of compound **16** (1.18 g, 2 mmol) in 9 mL of 1,2-dichloroethane was added compound **26** (830 mg, 2.2 mmol) and  $\text{MgSO}_4$  (80 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (0.34 mL, 6 mmol) and sodium cyanoborohydride (251mg, 4 mmol) were added. The reaction mixture was stirred at room temperature for 2 h under argon. Then aqueous  $\text{NaHCO}_3$  (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **28** (880 mg, 50 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J$  = 8.7 Hz, 2H), 7.35-7.16 (m, 9H), 6.99 (d,  $J$  = 8.7 Hz, 2H), 5.64 (d,  $J$  = 5.4 Hz, 1H), 5.03-4.85 (m, 3H), 4.24 -3.67 (m overlapping s, 15H), 3.14-2.70 (m, 9H), 2.39-2.28 (m, 2H), 1.85-1.51 (m, 5H), 1.29-1.25 (m, 3H), 0.93-0.78 (m, 9H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.2; MS (ESI) 912 (M+Na).

#### Example P8F

Compound **29**: To a stirred solution of compound **16** (857 g, 1.45 mmol) in 7 mL of 1,2-dichloroethane was added compound **27** (600 mg, 1.6 mmol) and  $\text{MgSO}_4$  (60 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (0.23 mL, 3 mmol) and sodium cyanoborohydride (183mg, 2.9 mmol) were added. The reaction mixture was stirred at room temperature for 2 h under argon. Then aqueous  $\text{NaHCO}_3$  (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **29** (650 mg, 50 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.7 Hz, 2H), 7.35-7.16 (m, 9H), 7.00 (d,  $J$  = 8.7 Hz, 2H), 5.64 (d,  $J$  = 5.4 Hz, 1H), 5.03-4.90 (m, 3H), 4.17 -3.67 (m overlapping s, 15H), 3.16-2.77 (m, 9H), 2.26-2.19 (m, 2H), 1.94-1.53 (m, 5H), 1.26-1.18 (m, 3H), 1.00-0.87 (m, 9H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  27.4; MS (ESI) 912 (M+Na).

**Scheme P9**



#### Example P9A

Compound **31**: To a stirred solution of compound **30** (20 g, 60 mmol) in 320 mL of toluene at room temperature under N<sub>2</sub> was added thionyl chloride (17.5 mL, 240 mmol) and a few drops of DMF. The resulted mixture was stirred at 60-70°C for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 280 mL of DCM, followed by TEA (50 mL, 360 mmol) and (S) lactate ethyl ester (17 mL, 150 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM / EtOAc, 1:1) to give **31** (24 g, 92 %) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 28.2 and 26.2; MS (ESI) 458 (M+Na).

#### Example P9B

Compound **32**: Compound **31** was purified using a Dynamax SD-200 HPLC system. The mobile phase consisted of acetonitrile: water (60:40, v/v) at a flow rate of 70 mL/ min. The injection volume was 3 mL. The detection was by fluorescence at 245 nm and peak area ratios were used for quantitations. Retention time was 8.1 min for compound **32** as yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 28.2; MS (ESI) 458 (M+Na).

#### Example P9C

Compound **33** was purified in the same manner and retention time was 7.9 min for compound **33** as yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 26.2; MS (ESI) 458 (M+Na).

#### Example P9D

Compound **34**: A solution of compound **33** (3.2 g) was dissolved in 60 mL of EtOH, then 0.9 mL of acetic acid and 10 % Pd/C (640 mg) was added. The resulted mixture was stirred under H<sub>2</sub> atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated

under reduced pressure to afford the compound **34** (2.7 g, 99 %) as a colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.42-7.18 (m, 5H), 6.10 (s, 1H), 5.15-5.02 (m, 1H), 4.24-4.05 (m, 2H), 3.25-3.16 (m, 2H), 2.36-2.21 (m, 2H), 1.61-1.58 (m, 3H), 1.35- 1.18, m, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.1; MS (ESI) 302 (M+1).

#### Example P9E

Compound **35**: To a stirred solution of compound **16** (8.9 g, 15 mmol) in 70 mL of 1,2-dichloroethane was added compound **34** (8.3 g, 23 mmol) and  $\text{MgSO}_4$  (80 mg), the resulted mixture was stirred at room temperature under argon for 2.5h, then acetic acid (3 mL, 52.5 mmol) and sodium cyanoborohydride (1.9g, 30 mmol) were added. The reaction mixture was stirred at room temperature for 1.5 h under argon. Then aqueous  $\text{NaHCO}_3$  (100 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel ( $\text{EtOH/EtOAc}$ , 1/9) to give **35** (8.4 g, 64 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J$  = 8.7 Hz, 2H), 7.36-7.17(m, 9H), 7.00 (d,  $J$  = 8.7 Hz, 2H), 5.64 (d,  $J$  = 5.1 Hz, 1H), 5.07-4.97 (m, 3H), 4.19 -3.67 (m overlapping s, 13H), 3.15-2.78 (m, 9H), 2.25-2.19 (m, 2H), 1.91-1.54 (m, 6H), 1.24-1.20 (m, 3H), 0.94-0.87 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  27.4; MS (ESI) 876 (M+1).

#### Resolution of Compound 35 Diastereomers

Analysis was performed on an analytical Daicel Chiralcel OD column, conditions described below, with a total of about 3.5 mg compound **35** free base injected onto the column. This lot was about a 3:1 mixture of major to minor diastereomers where the lactate ester carbon is a 3:1 mix of R and S configurations.

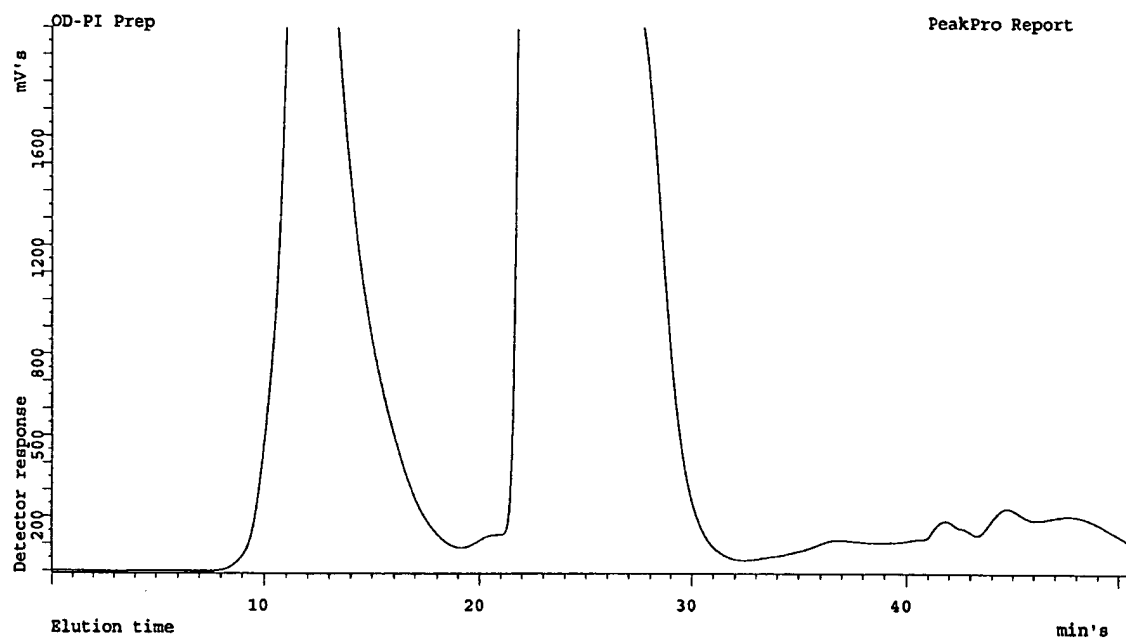
Two injections of 3.8 and 3.5 mg each were made using the conditions described below. The isolated major diastereomer fractions were evaporated to dryness on a rotary evaporator under house vacuum. The chromatographic solvents were displaced by two portions of ethyl acetate followed by a single portion of ethyl acetate – trifluoroacetic acid (about 95:5) and a final high vacuum strip to aid in removal of trace solvents. This yielded the major diastereomer trifluoroacetate salt as a gummy solid.

The resolved minor diastereomer was isolated for biological evaluation by an 11 mg injection, performed on an analytical Daicel Chiralcel OD column, using the conditions

described in below. The minor diastereomer of **35** was isolated as the trifluoroacetate salt by the conditions described above.

Larger scale injections (~ 300 mg **35** per injection) were later performed on a Daicel Chiralcel OD column semi-preparative column with a guard column, conditions described below. A minimal quantity of isopropyl alcohol was added to heptane to dissolve the 3:1 diastereomeric mix of **35** and the resolved diastereomers sample, and the isolated fractions were refrigerated until the eluted mobile phase was stripped.

Analytical Column, ~ 4 mg Injection, Heptane – EtOH (20:80) Initial



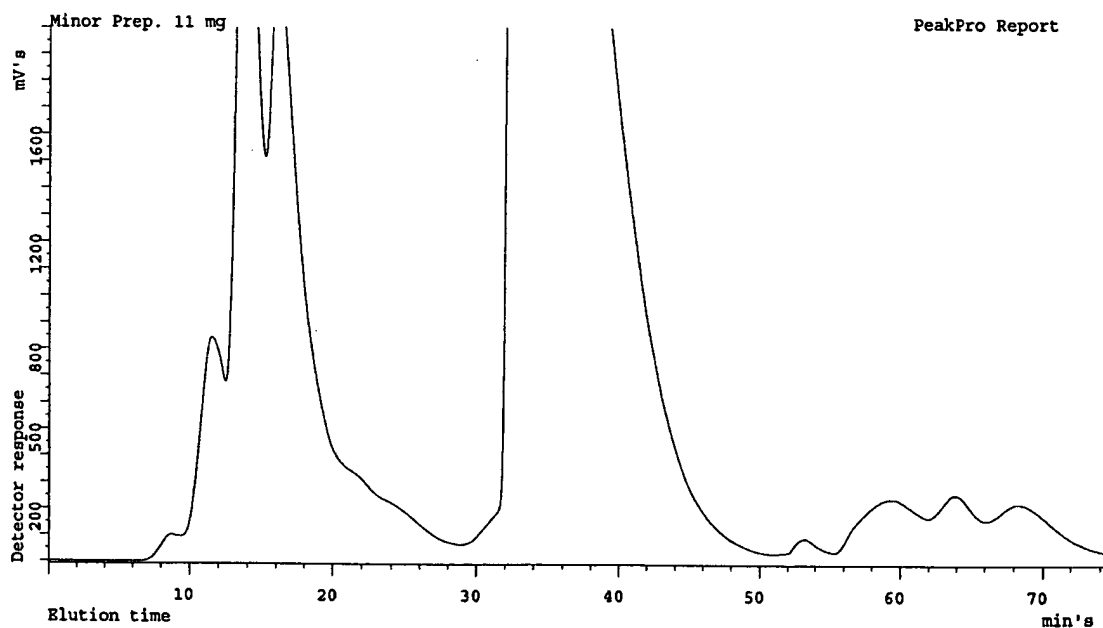
## HPLC CONDITIONS

Column : Chiralcel OD, 10  $\mu$ m, 4.6 x 250 mm  
Mobile Phase : Heptane – Ethyl Alcohol (20:80 initial)  
: 100% Ethyl Alcohol (final)

A. Note: Final began after first peak  
eluted

Flow Rate : 1.0 mL/min  
Run Time : As needed  
Detection : UV at 250 nm  
Temperature : Ambient  
Injection : ~ 4 mg on Column  
Sample Prep. : Dissolved in ~ 1 mL heptane –  
ethyl alcohol (50:50)  
Retention Times : 35 Minor ~ 14 min  
: 35 Major ~ 25 min

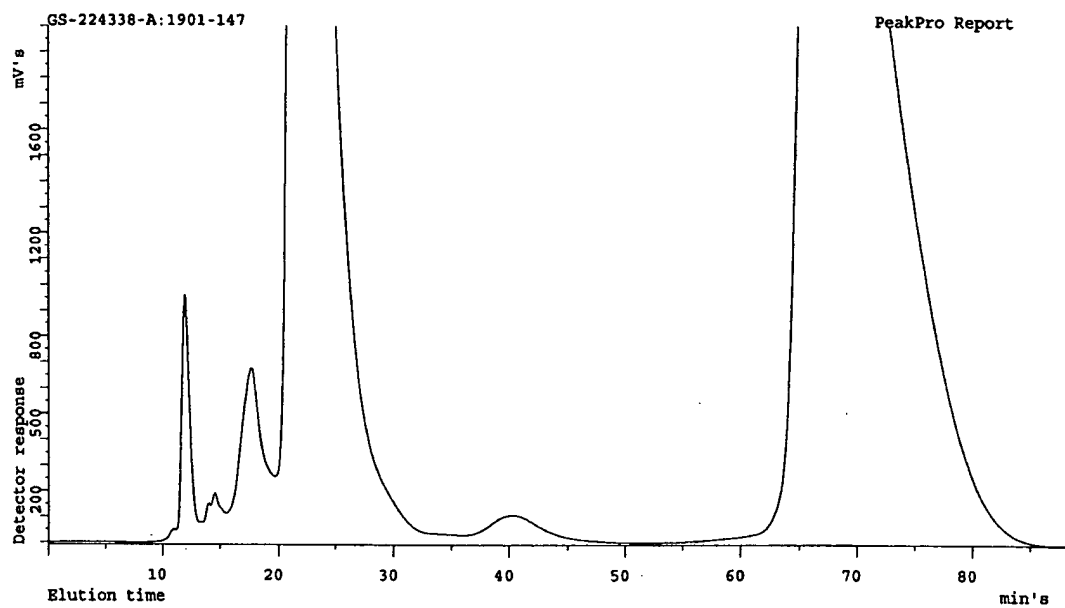
Analytical Column, ~ 6 mg Injection, Heptane – EtOH (65:35) Initial



## HPLC CONDITIONS

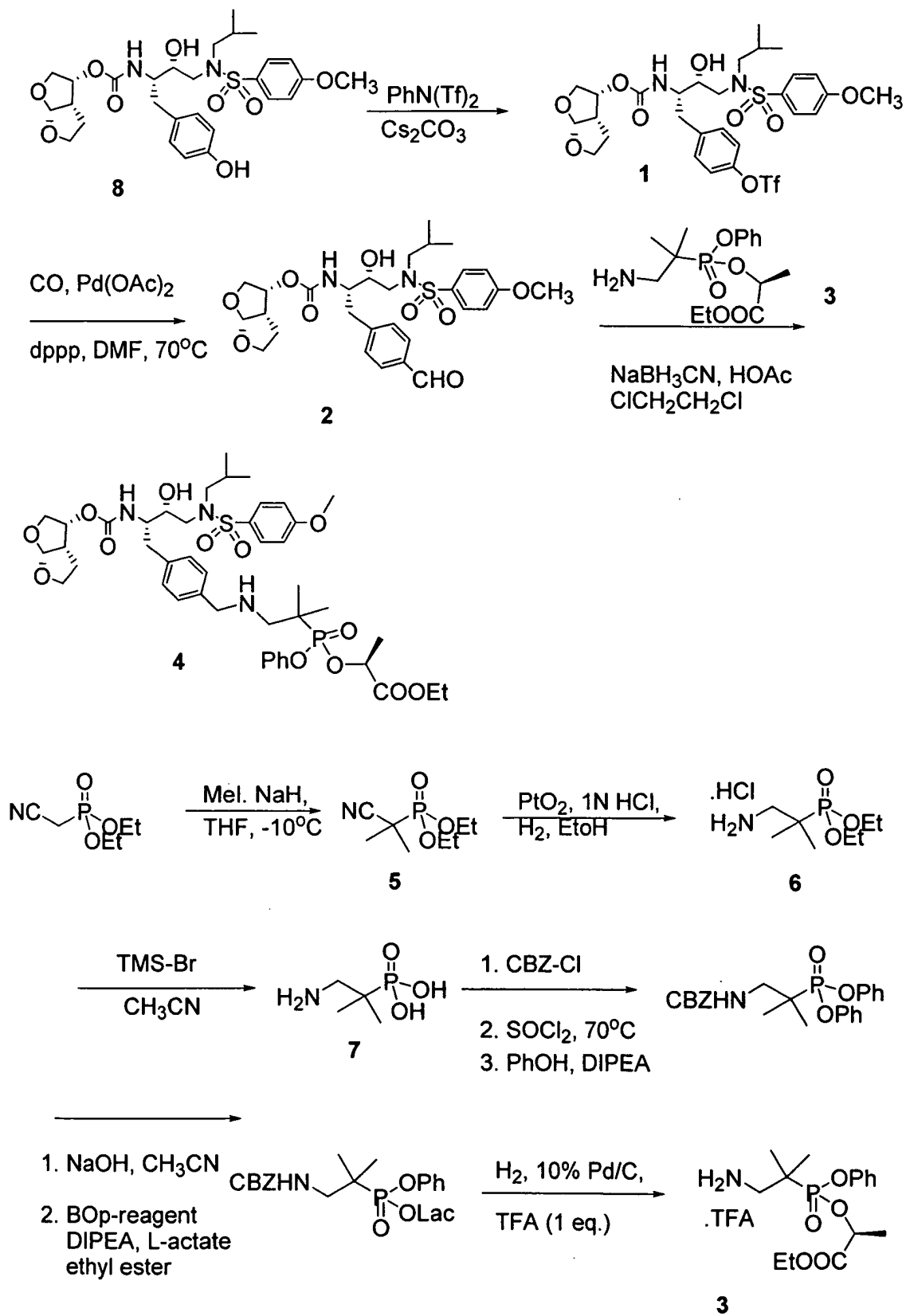
Column	: Chiralcel OD, 10 $\mu$ m, 4.6 x 250 mm
Mobile Phase	: Heptane – Ethyl Alcohol (65:35 initial) : Heptane – Ethyl Alcohol (57.5:42.5 intermediate) Note: Intermediate began after impurity peaks eluted  : Heptane – Ethyl Alcohol (20:80 final) Note: Final mobile phase began after minor diastereomer eluted
Flow Rate	: 1.0 mL/min
Run Time	: As needed
Detection	: UV at 250 nm
Temperature	: Ambient
Injection	: ~ 4 mg on Column
Sample Prep.	: Dissolved in ~ 1 mL heptane – ethyl alcohol (50:50)
Retention Times	: 35 Minor ~ 14 min : 35 Major ~ 40 min

Semi-Preparative Column, ~ 300 mg Injection, Heptane – EtOH (65:35) Initial



## HPLC CONDITIONS

Columns	: Chiralcel OD, 20 $\mu$ m, 21 x 50 mm (guard) : Chiralcel OD, 20 $\mu$ m, 21 x 250 mm
Mobile Phase	: Heptane – Ethyl Alcohol (65:35 initial) : Heptane – Ethyl Alcohol (50:50 intermediate) Note: Intermediate began after minor diastereomer peak eluted  : Heptane – Ethyl Alcohol (20:80 final) Note: Final mobile phase began after major diastereomer began to elute
Flow Rate	: 10.0 mL/min
Run Time	: As needed
Detection	: UV at 260 nm
Temperature	: Ambient
Injection	: ~ 300 mg on Column
Sample Prep.	: Dissolved in ~ 3.5 mL heptane – ethyl alcohol (70:30)
Retention Times	: 35 Minor ~ 14 min : 35 Major ~ 40 min



### Example P31

Triflate derivative 1: A THF-CH<sub>2</sub>Cl<sub>2</sub> solution (30mL-10 mL) of 8 (4 g, 6.9 mmol), cesium carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give crude triflate derivative 1.

Aldehyde 2: Crude triflate 1 (4.5 g, 6.9 mmol) was dissolved in DMF (20 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). Pd(OAc)<sub>2</sub> (0.12 g, 0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added, the solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution, then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4 mL, 38 mmol), and triethylsilane (3 ml), 18 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was worked up, and purified on silica gel column chromatograph to afford aldehyde 2 (2.1 g, 51 %). (Hostetler, *et al. J. Org. Chem.*, 1999. 64, 178-185).

Lactate prodrug 4: Compound 4 is prepared as described above procedure for Example 9E, Compound 35 by the reductive amination between 2 and 3 with NaBH<sub>3</sub>CN in 1,2-dichloroethane in the presence of HOAc.

### Example P32

#### Preparation of Compound 3

Diethyl (cyano(dimethyl)methyl) phosphonate 5: A THF solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmol) was cooled to -10°C, followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and iodomethane (17 g, 112 mmol). The resulting solution was stirred at -10°C for 2 hr, then 0°C for 1 hr, was worked up, and purified to give dimethyl derivative 5 (5 g, 86 %).

Diethyl (2-amino-1,1-dimethyl-ethyl)phosphonate 6: Compound 5 was reduced to amine derivative 6 by the described procedure (*J. Med. Chem.* 1999, 42, 5010-5019).

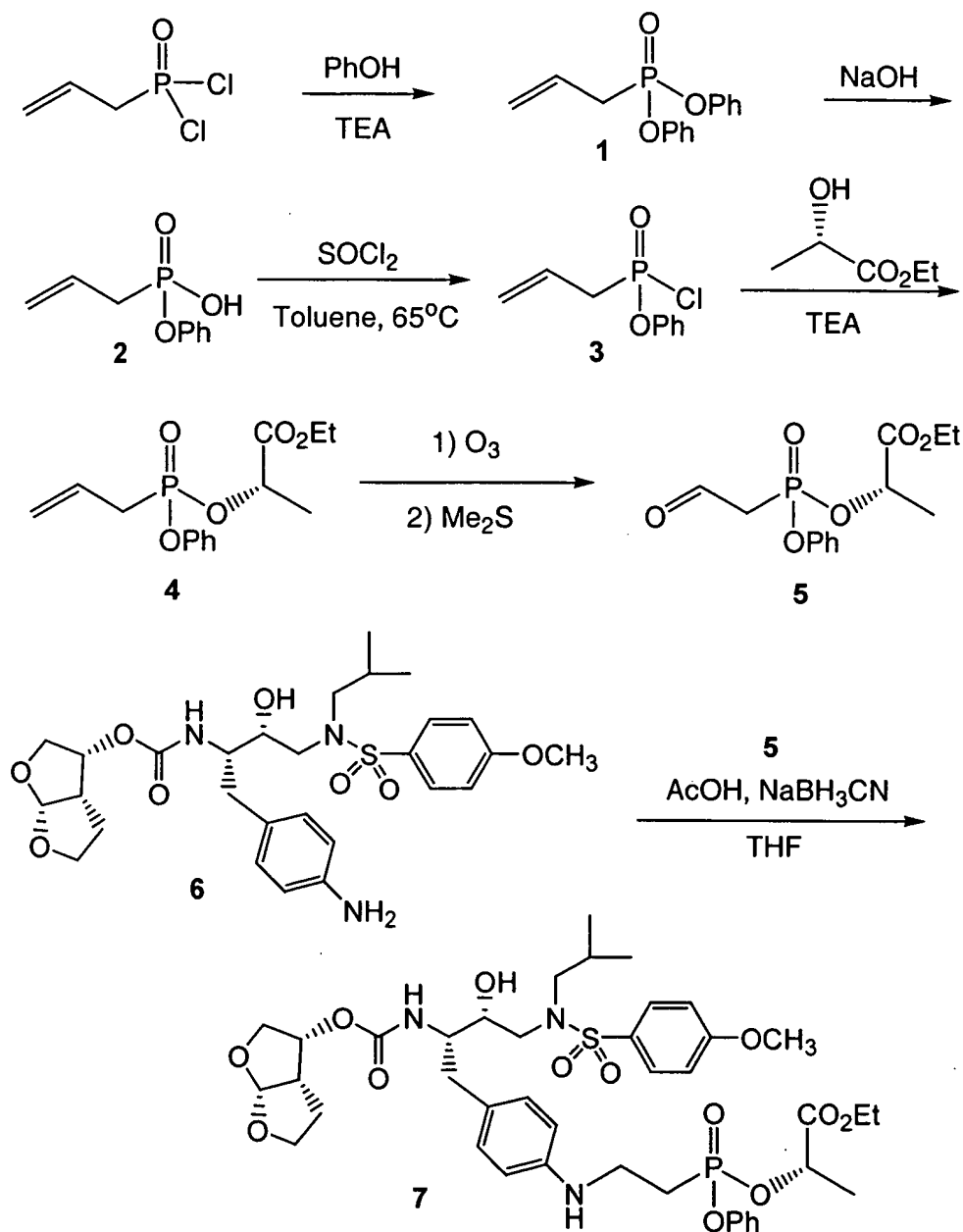
A solution of ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of 5 (2.2 g, 10.7 mmol) was hydrogenated at 1 atmosphere in the presence of PtO<sub>2</sub> (1.25 g) at room temperature overnight. The catalyst was filtered through a celite pad. The filtrate was concentrated to dryness, to give crude 6 (2.5g, as HCl salt).

**2-Amino-1,1-dimethyl-ethyl phosphonic acid 7:** A solution of CH<sub>3</sub>CN (30 mL) of crude **6** (2.5 g) was cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude **7** which was used for next reaction without further purification.

**Lactate phenyl (2-amino-1,1-dimethyl-ethyl)phosphonate 3:** Compound **3** is synthesized according to the procedures described in Example 9D, Compound **34** for the preparation of lactate phenyl 2-aminoethyl phosphonate **34**. Compound **7** is protected with CBZ, followed by the reaction with thionyl chloride at 70°C. The CBZ protected dichlorodate is reacted phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonate derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10 % Pd/C and 1 eq. of TFA affords compound **3** as TFA salt.

## Example Section Q

### Scheme Q1



### Example Q1

**Monophenol Allylphosphonate 2:** To a solution of allylphosphonic dichloride (4 g, 25.4 mmol) and phenol (5.2 g, 55.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) at  $0^\circ\text{C}$  was added TEA (8.4 mL, 60 mmol). After stirred at room temperature for 1.5 h, the mixture was diluted with hexane-ethyl

acetate and washed with HCl (0.3 N) and water. The organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (eluted with 2:1 hexane-ethyl acetate) to afford crude product diphenol allylphosphonate **1** (7.8 g, containing the excessive phenol) as an oil which was used directly without any further purification. The crude material was dissolved in  $\text{CH}_3\text{CN}$  (60 mL), and NaOH (4.4N, 15 mL) was added at  $0^\circ\text{C}$ . The resulted mixture was stirred at room temperature for 3 h, then neutralized with acetic acid to  $\text{pH} = 8$  and concentrated under reduced pressure to remove most of the acetonitrile. The residue was dissolved in water (50 mL) and washed with  $\text{CH}_2\text{Cl}_2$  (3X25 mL). The aqueous phase was acidified with concentrated HCl at  $0^\circ\text{C}$  and extracted with ethyl acetate. The organic phase was dried over  $\text{MgSO}_4$ , filtered, evaporated and co-evaporated with toluene under reduced pressure to yield desired monophenol allylphosphonate **2** (4.75 g, 95%) as an oil.

#### Example Q2

Monolactate Allylphosphonate **4**: To a solution of monophenol allylphosphonate **2** (4.75 g, 24 mmol) in toluene (30 mL) was added  $\text{SOCl}_2$  (5 mL, 68 mmol) and DMF (0.05 mL). After stirred at  $65^\circ\text{C}$  for 4 h, the reaction was completed as shown by  $^{31}\text{P}$  NMR. The reaction mixture was evaporated and co-evaporated with toluene under reduced pressure to give mono chloride **3** (5.5 g) as an oil. To a solution of chloride **3** in  $\text{CH}_2\text{Cl}_2$  (25 mL) at  $0^\circ\text{C}$  was added ethyl (s)-lactate (3.3 mL, 28.8 mmol), followed by TEA. The mixture was stirred at  $0^\circ\text{C}$  for 5 min then at room temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N), the organic phase was washed with water, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford desired monolactate **4** (5.75 g, 80%) as an oil (2:1 mixture of two isomers):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.1-7.4 (m, 5H), 5.9 (m, 1H), 5.3 (m, 2H), 5.0 (m, 1H), 4.2 (m, 2H), 2.9 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.4, 23.9.

#### Example Q3

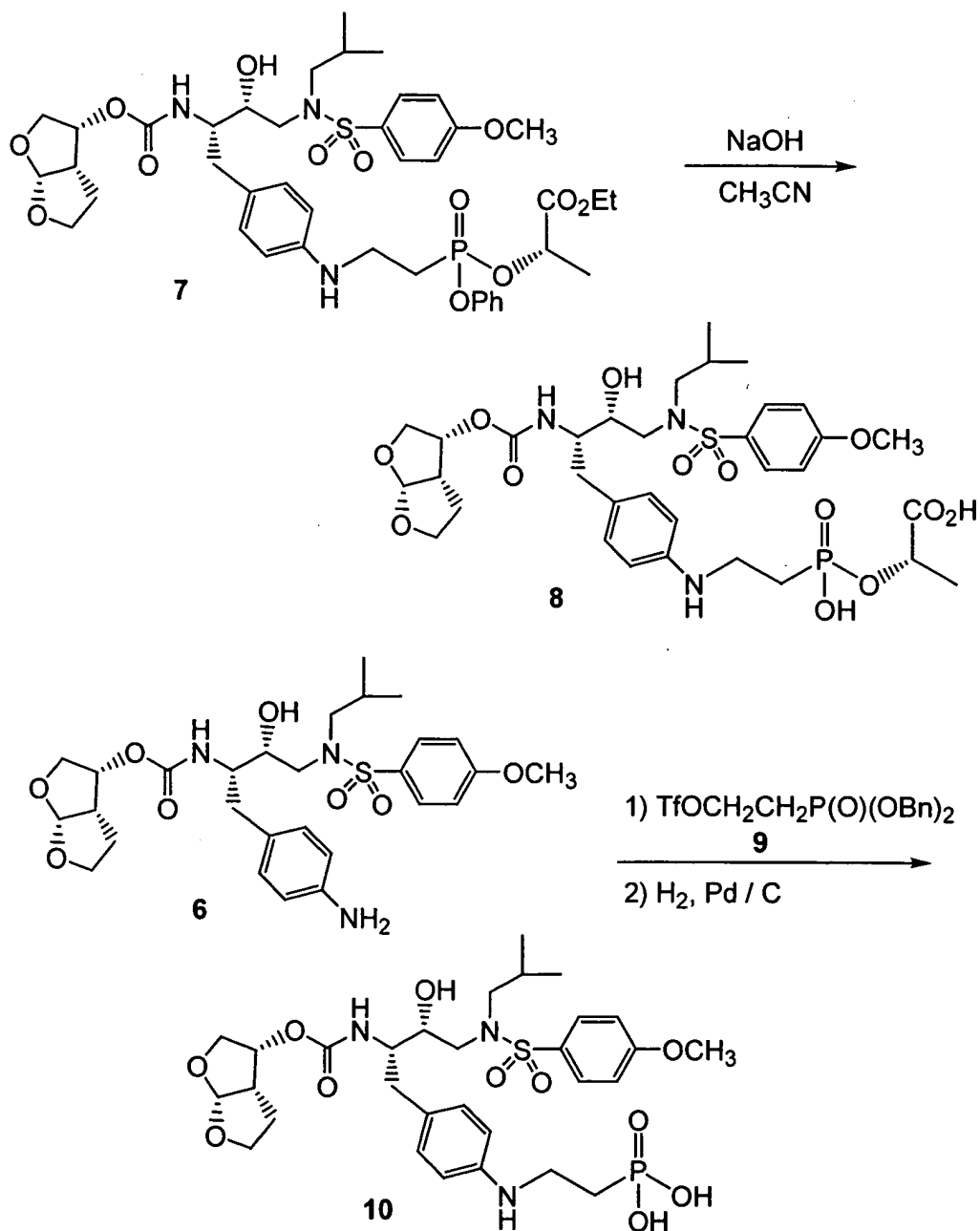
Aldehyde **5**: A solution of allylphosphonate **4** (2.5 g, 8.38 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was bubbled with ozone air at  $-78^\circ\text{C}$  until the solution became blue, then bubbled with nitrogen until the blue color disappeared. Methyl sulfide (3 mL) was added at  $-78^\circ\text{C}$ . The mixture was warmed up to room temperature, stirred for 16 h and concentrated under reduced pressure to give

desired aldehyde **5** (3.2 g, as a 1:1 mixture of DMSO):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.8 (m, 1H), 7.1-7.4 (m, 5H), 5.0 (m, 1H), 4.2 (m, 2H), 3.4 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.7, 15.4.

#### Example Q4

Compound **7**: To a solution of aniline **6** (reported before) (1.62 g, 2.81 mmol) in THF (40 mL) was added acetic acid (0.8 mL, 14 mmol), followed by aldehyde **5** (1.3 g, 80%, 3.46 mmol) and  $\text{MgSO}_4$  (3 g). The mixture was stirred at room temperature for 0.5 h, then  $\text{NaBH}_3\text{CN}$  (0.4 g, 6.37 mmol) was added. After stirred for 1 h, the reaction mixture was filtered. The filtrate was diluted with ethyl acetate and washed with  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give compound **6** (1.1 g, 45%) as a 3:2 mixture of two isomers, which were separated by HPLC (mobile phase, 70%  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ ; flow rate: 70 mL/min; detection: 254 nm; column:  $8\mu\text{C}18$ , 41X250 mm, Varian). Isomer A (0.39 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (d, 2H), 7.1-7.4 (m, 5H), 7.0 (m, 4H), 6.6 (d, 2H), 5.65 (d, 1H), 5.05 (m, 2H), 4.9 (d, 1H), 4.3 (brs, 1H), 4.2 (q, 2H), 3.5-4.0 (m, 6H), 3.9 (s, 3H), 2.6-3.2 (m, 9H), 2.3 (m, 2), 1.6-1.9 (m, 5H), 1.25 (t, 3H), 0.9 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.5; MS (ESI): 862 (M+H). Isomer B (0.59 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (d, 2H), 7.1-7.4 (m, 5H), 7.0 (m, 4H), 6.6 (d, 2H), 5.65 (d, 1H), 5.05 (m, 2H), 4.9 (d, 1H), 4.5 (brs, 1H), 4.2 (q, 2H), 3.5-4.0 (m, 6H), 3.9 (s, 3H), 2.7-3.2 (m, 9H), 2.4 (m, 2), 1.6-1.9 (m, 2H), 1.4 (d, 3H), 1.25 (t, 3H), 0.9 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.4; MS (ESI): 862 (M+H).

## Scheme Q2



## Example Q5

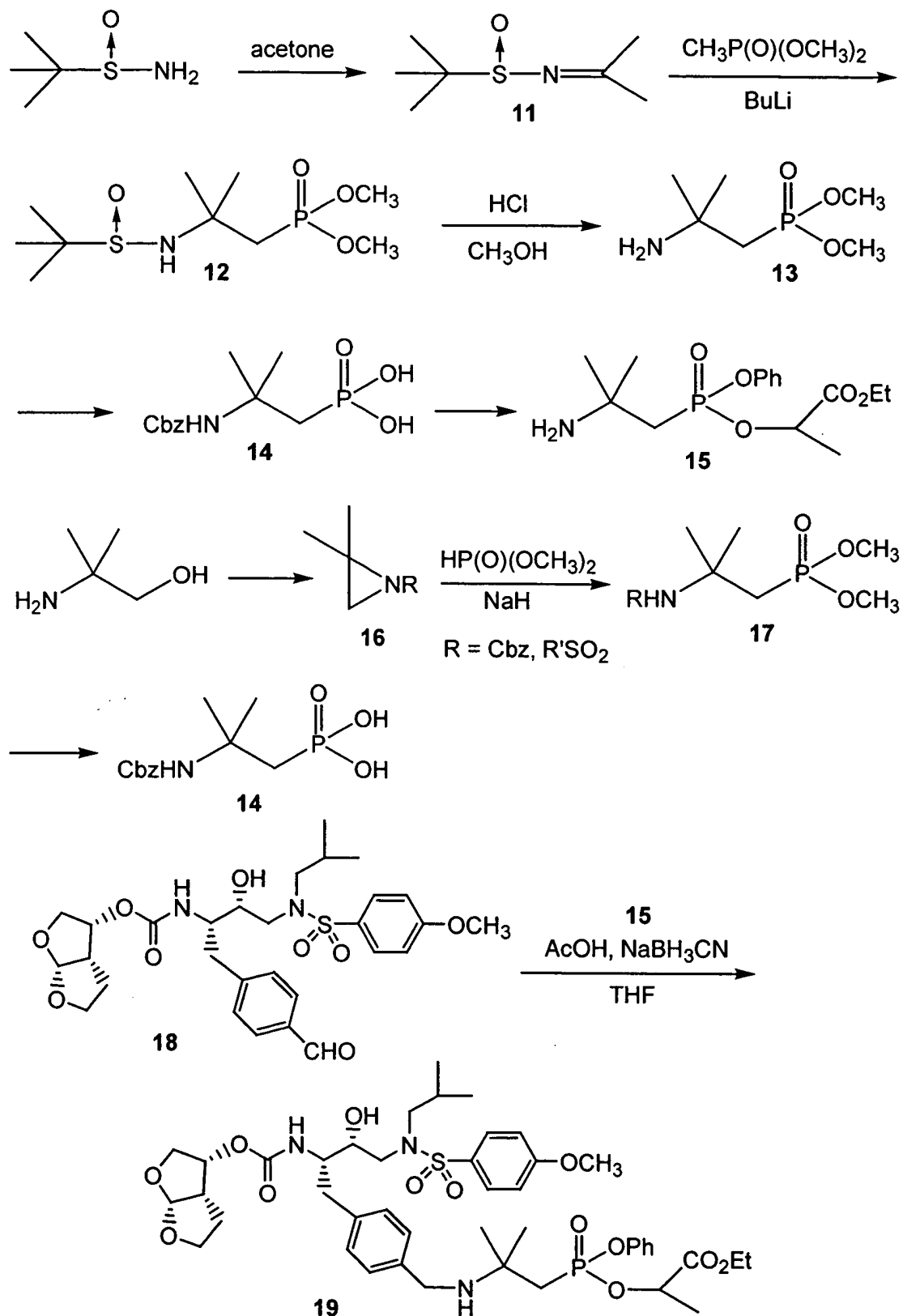
Acid **8**: To a solution of compound **7** (25 mg, 0.029 mmol) in acetonitrile (1 mL) at 0°C was added NaOH (1N, 0.125 mL). The mixture was stirred at 0°C for 0.5 h and at room temperature for 1 h. The reaction was quenched with acetic acid and purified by HPLC to give acid **8** (10 mg, 45%). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.8 (d, 2H), 7.5 (d, 2H), 7.4 (d, 2H), 7.1 (d, 2H), 5.6

(d, 1H), 4.9 (m, 3H), 3.2-4.0 (m, 6H), 3.9 (s, 3H), 2.6-3.2 (m, 9H), 2.05 (m, 2), 1.4-1.7 (m, 2H), 1.5 (d, 3H), 0.9 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  20.6; MS (ESI): 758 (M+H).

#### Example Q6

**Diacid 10:** To a solution of triflate **9** (94 mg, 0.214 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added a solution of aniline **6** (100 mg, 0.173 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at  $-40^\circ\text{C}$ , followed by 2,6-lutidine (0.026 mL). The mixture was warmed up to room temperature and stirred for 1 h. Cesium carbonate (60 mg) was added and the reaction mixture was stirred for additional 1 h. The mixture was diluted with ethyl acetate, washed with HCl (0.2N), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by HPLC to afford dibenzyl phosphonate (40 mg). To a solution of this dibenzyl phosphonate in ethanol (3 mL) and ethyl acetate (1 mL) was added 10% Pd/C (40 mg). The mixture was stirred under hydrogen atmosphere (balloon) for 4 h. The reaction mixture was diluted with methanol, filtered and concentrated under reduced pressure. The residue was washed with ethyl acetate and dried to give desired product diacid **10** (20 mg).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.8 (d, 2H), 7.3 (d, 2H), 7.1 (2d, 4H), 5.6 (d, 1H), 4.9 (m, 2H), 3.4-4.0 (m, 6H), 3.9 (s, 3H), 2.5-3.2 (m, 9H), 2.0 (m, 2), 1.4-1.7 (m, 2H), 0.9 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  22.1; MS (ESI): 686 (M+H).

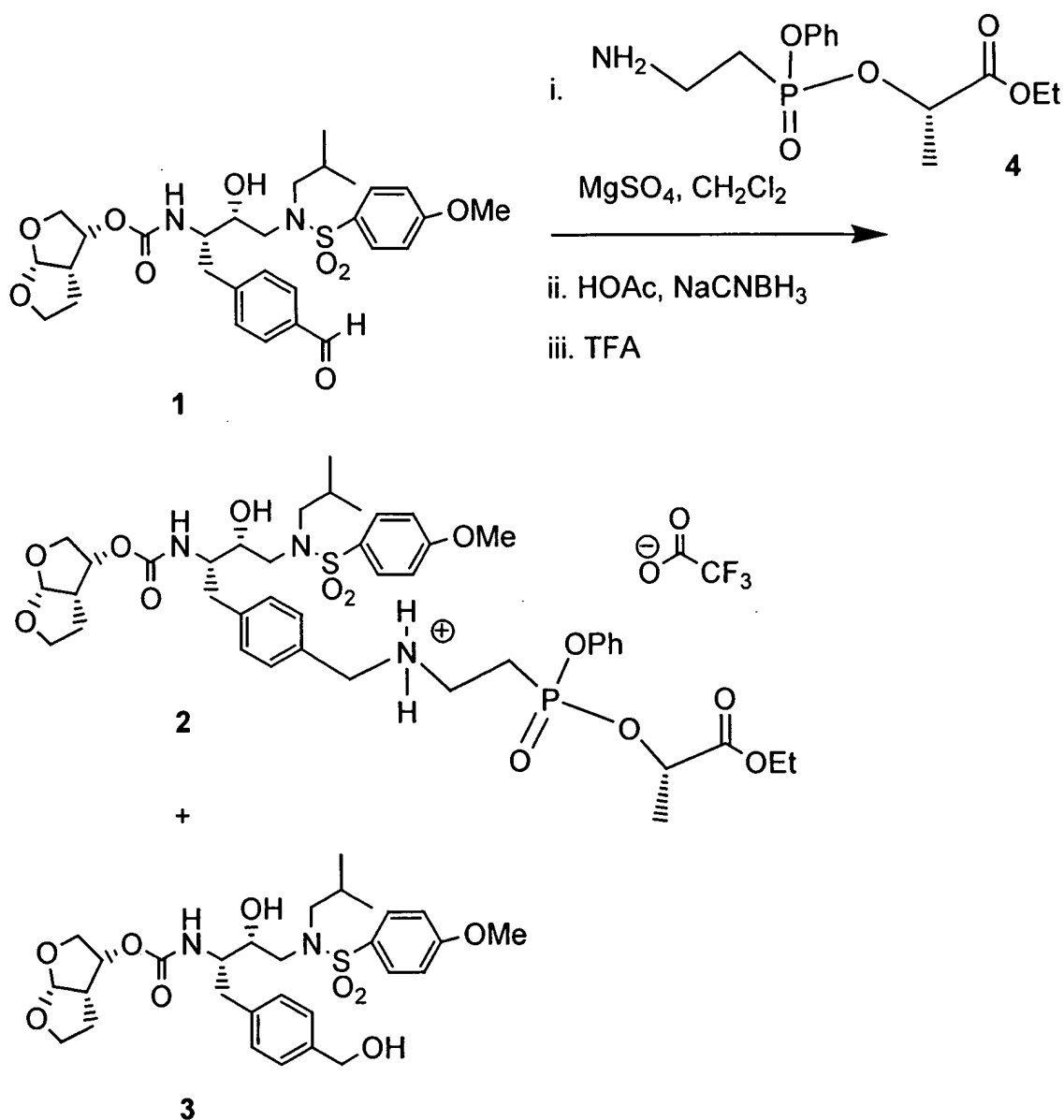
**Scheme Q3**



The synthesis of compound **19** is outlined in Scheme Q3. Condensation of 2-methyl-2-propanesulfinamide with acetone give sulfinyl imine **11** (*J. Org. Chem.* 1999, 64, 12). Addition of dimethyl methylphosphonate lithium to **11** afford **12**. Acidic methanolysis of **12** provide amine **13**. Protection of amine with Cbz group and removal of methyl groups yield phosphonic acid **14**, which can be converted to desired **15** using methods reported earlier on. An alternative synthesis of compound **14** is also shown in Scheme Q3. Commercially available 2-amino-2-methyl-1-propanol is converted to aziridines **16** according to literature methods (*J. Org. Chem.* 1992, 57, 5813; and *Syn. Lett.* 1997, 8, 893). Aziridine opening with phosphite give **17** (*Tetrahedron Lett.* 1980, 21, 1623). Deprotection (and, if necessary, reprotection) of **17** afford **14**. Reductive amination of amine **15** and aldehyde **18** provides compound **19**.

## Example Section R

### Scheme R1



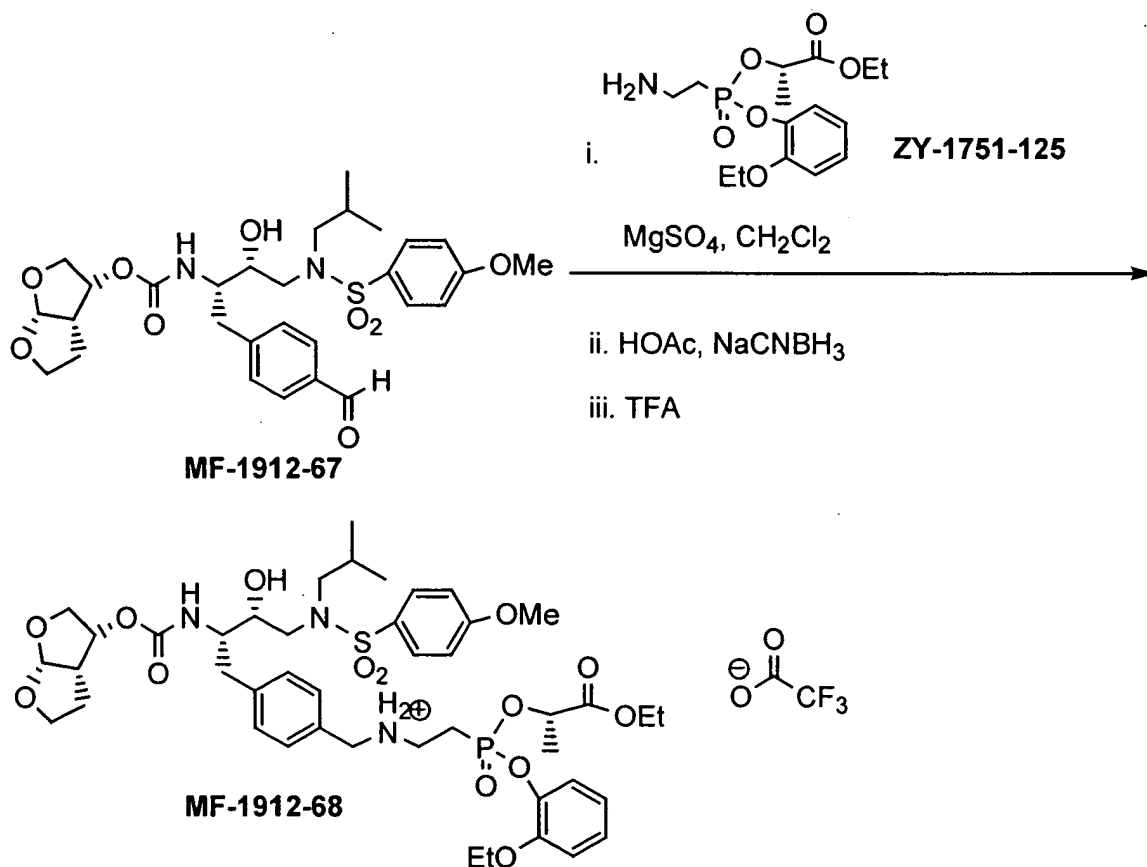
### Example R1

2-{[2-(4-{2-(Hexahydro-furo[2,3-b]furan-3-yloxycarbonylamino)-3-hydroxy-4-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyl}-benzylamino)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester **2** (Compound 35, previous Example 9E).

A solution of **1** (2.07 g, 3.51 mmol) and **4** (1.33 g, 3.68 mmol) of a 4:1 mixture of two diastereomers at the phosphorous center) were dissolved in 14 mL of  $(\text{CH}_2\text{Cl}_2)_2$  to provide a

clear solution. Addition of  $\text{MgSO}_4$  (100 mg) to the solution resulted in a white cloudy mixture. The solution was stirred at ambient temperature for 3 hours when acetic acid (0.80 mL, 14.0 mmol) and sodium cyanoborohydride (441 mg, 7.01 mmol) were added. Following the reaction progress by TLC showed complete consumption of the aldehyde starting materials in 1 hour. The reaction mixture was worked up by addition of 200 mL of saturated aqueous  $\text{NaHCO}_3$  and 400 mL of  $\text{CH}_2\text{Cl}_2$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  two more times (2 x 300 mL). The combined organic extracts were dried *in vacuo* and purified by column chromatography (EtOAc- 10% MeOH: EtOAc) to provide the desired product as a foam. The early eluting compound from the column was collected and characterized as alcohol **3** (810 mg, 39%). Addition of TFA (3 x 1 mL) generated the TFA salt which was lyophilized from 50 mL of a 1:1  $\text{CH}_3\text{CN}$ :  $\text{H}_2\text{O}$  to provide 1.63 g (47%) of the product **2** as a white powder.  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  8.23 (br s, 2H), 7.79 (d,  $J$  = 8.4 Hz, 2H), 7.45- 7.13 (m, 9H), 7.09 (d,  $J$  = 8.4 Hz, 2H), 5.86 (d,  $J$  = 9.0 Hz, 1H), 5.55 (d,  $J$  = 4.8 Hz, 1H), 5.05-4.96 (m, 1H), 4.96- 4.88 (m, 1H), 4.30-4.15 (m, 4H), 3.89 (s, 3H), 3.86- 3.76 (m, 4H), 3.70- 3.59 (m, 4H), 3.56- 3.40 (m, 2H), 3.34 (d,  $J$  = 15 Hz, 1H), 3.13 (d,  $J$  = 13.5 Hz, 1H), 3.06- 2.93 (m, 2H), 2.92- 2.80 (m, 2H), 2.69- 2.43 (m, 3H), 2.03- 1.86 (m, 1H), 1.64- 1.48 (m, 1H), 1.53 and 1.40 (d,  $J$  = 6.3 Hz,  $J$  = 6.6 Hz, 3H), 1.45- 1.35 (m, 1H), 1.27 and 1.23 (t,  $J$  = 6.9 Hz,  $J$  = 7.2 Hz, 3H), 0.90 (t,  $J$  = 6.9 Hz, 6H).  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  24.47, 22.86. ESI ( $\text{M} + \text{H}$ ) $^+$  876.4.

## Example R2



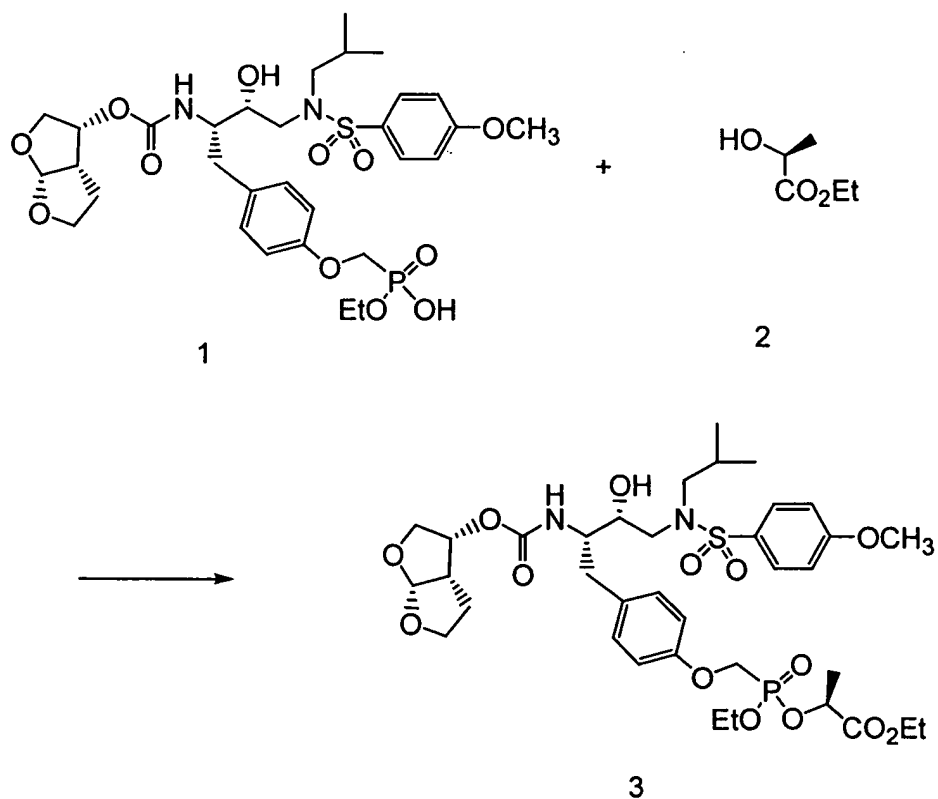
2-{{2-(4-{2-(Hexahydro-furo[2,3-b]furan-3-yloxycarbonylamino)-3-hydroxy-4-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyl}-benzylamino)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester (**MF-1912-68**):

A solution of **MF-1912-67** (0.466 g, 0.789 mmol) and **ZY-1751-125** (0.320 g, 0.789 mmol) of a 1:1 mixture of two diastereomers at the phosphorous center) were dissolved in 3.1 mL of  $(\text{CH}_2\text{Cl}_2)_2$  to provide a clear solution. Addition of  $\text{MgSO}_4$  (20 mg) to the solution resulted in a white cloudy mixture. The solution was stirred at ambient temperature for 3 hours when acetic acid (0.181 mL, 3.16 mmol) and sodium cyanoborohydride (99 mg, 1.58 mmol) were added. Following the reaction progress by TLC showed complete consumption of the aldehyde starting materials in 1.5 hour. The reaction mixture was worked up by addition of 50 mL of saturated aqueous  $\text{NaHCO}_3$  and 200 mL of  $\text{CH}_2\text{Cl}_2$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  two more times (2 x 200 mL). The combined organic extracts were dried *in vacuo* and purified by column chromatography (EtOAc- 10% MeOH: EtOAc) to provide the desired product as a foam. The early eluting compound from the column was collected and characterized to be MF-1912-

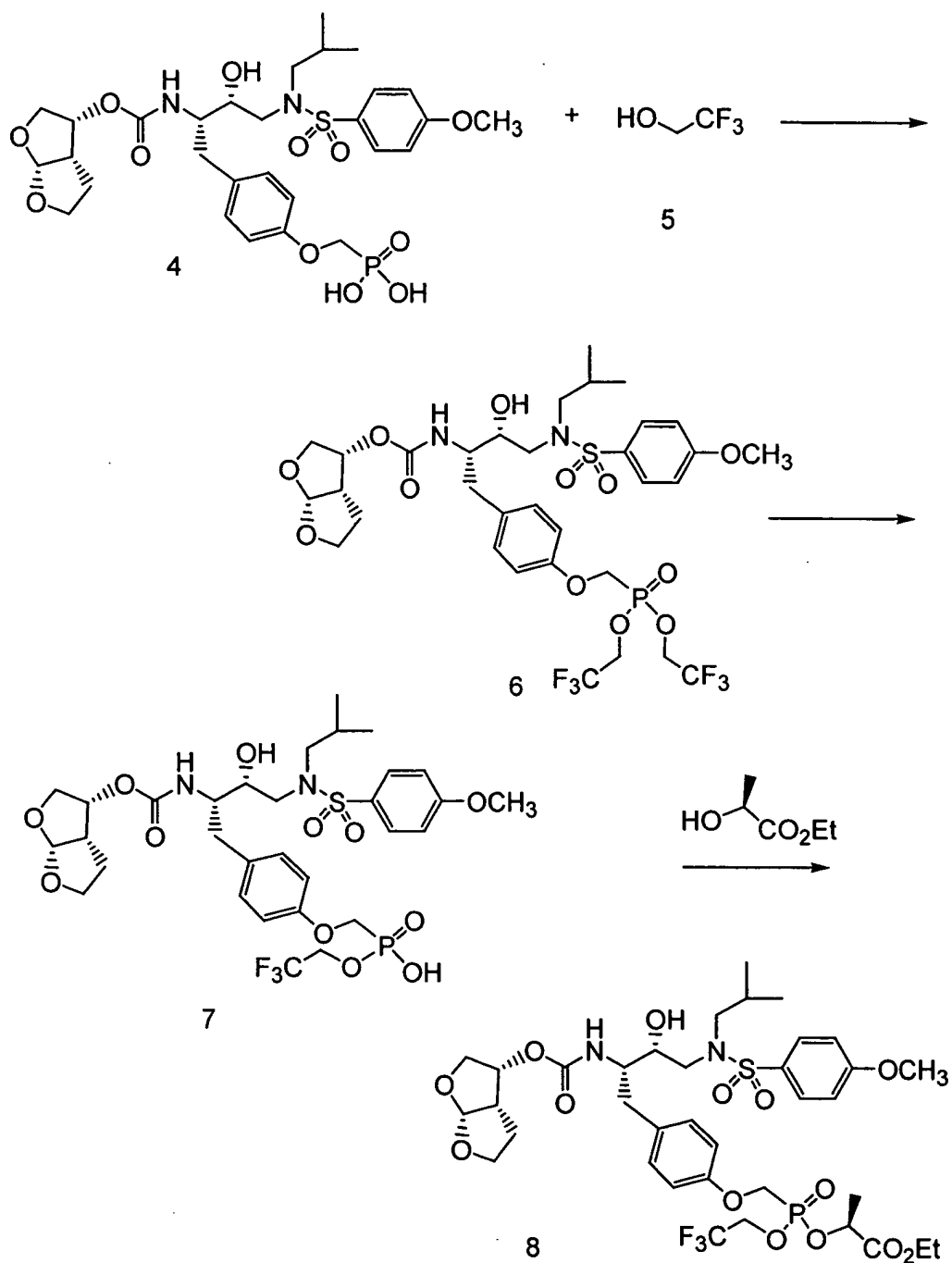
48b alcohol (190 mg, 41%). Addition of TFA (3 x 1 mL) generated the TFA salt which was lyophilized from 50 mL of a 1:1 CH<sub>3</sub>CN: H<sub>2</sub>O to provide 0.389 g (48%) of the product as a white powder. <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 8.39 (br s, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.26-7.16 (m, 2H), 7.10 (d, *J* = 9 Hz, 3H), 7.01- 6.92 (m, 1H), 5.78 (d, *J* = 9.0 Hz, 1H), 5.55 (d, *J* = 5.1 Hz, 1H), 5.25-5.03 (m, 1H), 4.95- 4.88 (m, 1H), 4.30- 4.17 (m, 4H), 4.16- 4.07 (m, 2H), 3.90 (s, 3H), 3.88-3.73 (m, 4H), 3.72- 3.60 (m, 2H), 3.57- 3.38 (m, 2H), 3.32 (br d, *J* = 15.3 Hz, 1H), 3.13 (br d, *J* = 14.7 Hz, 1H), 3.05- 2.92 (m, 2H), 2.92- 2.78 (m, 2H), 2.68- 2.48 (m, 3H), 2.03- 1.90 (m, 1H), 1.62- 1.51 (m, 1H), 1.57 and 1.46 (d, *J* = 6.9 Hz, *J* = 6.9 Hz, 3H), 1.36- 1.50 (m, 1H), 1.43- 1.35 (m, 4H), 1.33- 1.22 (m, 3H), 0.91 (t, *J* = 6.6 Hz, 6H). <sup>31</sup>P NMR (CD<sub>3</sub>CN) δ 25.27, 23.56. ESI (M+ H)<sup>+</sup> 920.5.

### Example Section S

Scheme S1



## Scheme S2



## Example S1

**Mono-Ethyl mono-lactate 3:** To a solution of 1 (96mg, 0.137 mmol) and ethyl lactate 2 (0.31 mL, 2.7 mmol) in pyridine (2 mL) was added N, N-dicyclohexylcarbodiimide (170 mg, 0.822 mmol). The solution was stirred for 18h at 70°C. The mixture was cooled to room temperature and diluted with dichloromethane. The solid was removed by filtration and the

filtrate was concentrated. The residue was suspended in diethyl ether/dichloromethane and filtered again. The filtrate was concentrated and mixture was chromatographed on silica gel eluting with EtOAc/hexane to provide compound 3 (43 mg, 40%) as a foam:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.00 (d, 2H); 7.00 (d, 2H), 6.88 (d, 2H), 5.67 (d, 1H), 4.93-5.07 (m, 2H), 4.15-4.39 (m, 6H), 3.70-3.99 (m, 10H), 2.76-3.13 (m, 7H), 1.55-1.85 (m, 9H), 1.23-1.41 (m, 6H), 0.90 (dd, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.1, 20.2; MS (ESI) 823 ( $\text{M}+\text{Na}$ ).

#### Example S2

Bis-2,2,2-trifluoroethyl phosphonate 6: To a solution of 4 (154mg, 0.228 mmol) and 222,-trifluoroethanol 5 (1 mL, 13.7 mmol) in pyridine (3 mL) was added N, N-dicyclohexylcarbodiimide (283 mg, 1.37 mmol). The solution was stirred for 6.5h at 70°C. The mixture was cooled to room temperature and diluted with dichloromethane. The solid was removed by filtration and the filtrate was concentrated. The residue was suspended in dichloromethane and filtered again. The filtrate was concentrated and mixture was chromatographed on silica gel eluting with EtOAc/hexane to provide compound 6 (133 mg, 70%) as a foam:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.21 (d, 2H); 7.00 (d, 2H), 6.88 (dd, 2H), 5.66 (d, 1H), 4.94-5.10 (m, 3H), 4.39-4.56 (m, 6H), 3.71-4.00 (m, 10H), 2.77-3.18 (m, 7H), 1.67-1.83(m, 2H), 0.91 (dd, 4H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.2; MS (ESI) 859 ( $\text{M}+\text{Na}$ ).

#### Example S3

Mono-2,2,2-trifluoroethyl phosphonate 7: To a solution of 6 (930mg, 1.11 mmol) in THF (14 mL) and water (10 mL) was added an aqueous solution of NaOH in water (1N, 2.2 mL). The solution was stirred for 1h at 0°C. An excess amount of Dowex resin ( $\text{H}^+$ ) was added to until pH=1. The mixture was filtered and the filtrate was concentrated under reduced pressure. The concentrated solution was azeotroped with EtOAc/toluene three times and the white powder was dried *in vacuo* provide compound 7 (830 mg, 100%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.11 (d, 2H); 6.99 (d, 2H), 6.85 (d, 2H), 5.63 (d, 1H), 5.26 (m, 1H), 5.02 (m, 1H), 4.40 (m, 1H), 4.14 (m, 4H), 3.60-3.95 (m, 12H), 2.62-3.15 (m, 15H), 1.45-1.84 (m, 3H), 1.29 (m, 4H), 0.89 (d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.9; MS (ESI) 723 ( $\text{M}+\text{Na}$ ).

#### Example S4

Mono-2,2,2-trifluoroethyl mono-lactate 8: To a solution of 7 (754mg, 1 mmol) and N, N-dicyclohexylcarbodiimide (1.237 g, 6 mmol) in pyridine (10 mL) was added ethyl lactate (2.26 mL, 20 mmol). The solution was stirred for 4.5h at 70°C. The mixture was concentrated and the residue was suspended in diethyl ether (5 mL) and dichloromethane (5 mL) and filtered. The solid was washed a few times with diethyl ether. The combined filtrate was concentrated and the crude product was chromatographed on silica gel, eluting with EtOAc and hexane to provide compound 8 (610 mg, 71%) as a foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, 2H), 7.16 (d, 2H); 6.99 (d, 2H), 6.88 (dd, 2H), 5.66 (d, 1H), 4.95-5.09 (m, 2H), 4.19-4.65 (m, 6H), 3.71-4.00 (m, 9H), 2.76-3.13 (m, 6H), 1.57-1.85 (m, 7H), 1.24-1.34 (m, 4H), 0.91 (dd, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.29, 21.58; MS (ESI) 855 (M+1).

#### Example Section T

##### Example T1

Boc-protected hydroxylamine 1: A solution of diethyl hydroxymethyl phosphonate triflate (0.582 g, 1.94 mmol) in dichloromethane (19.4 mL) was treated with triethylamine (0.541 mL, 3.88 mmol). Tert-butyl N-hydroxy-carbamate (0.284 g, 2.13 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NaCl, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 – ethyl acetate/hexane) affording the BOC-protected hydroxylamine 1 (0.41 g, 75%) as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.83 (s, 1H), 4.21 (d, 2H), 4.18 (q, 4H), 1.47 (s, 9H), 1.36 (t, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.3.

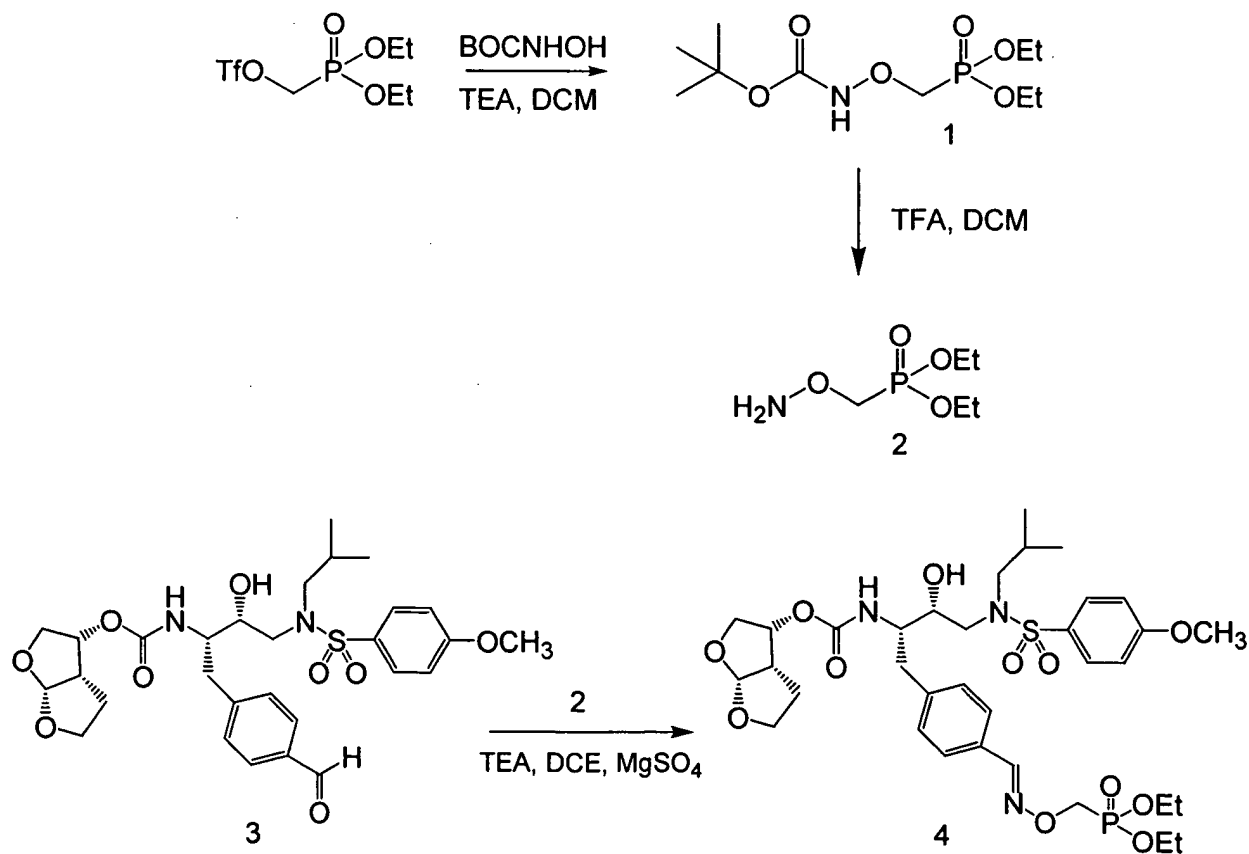
##### Example T2

Hydroxylamine 2: A solution of BOC-protected hydroxylamine 1 (0.305 g, 1.08 mmol) in dichloromethane (2.40 mL) was treated with trifluoroacetic acid (0.829 mL, 10.8 mmol). The reaction was stirred for 1.5 hours at room temperature and then the volatiles were evaporated under reduced pressure with toluene to afford the hydroxylamine 2 (0.318 g, 100%) as the TFA salt which was used directly without any further purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.87 (s, 2H), 4.45 (d, 2H), 4.24 (q, 4H), 1.38 (t, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 16.9; MS (ESI) 184 (M+H).

### Example T3

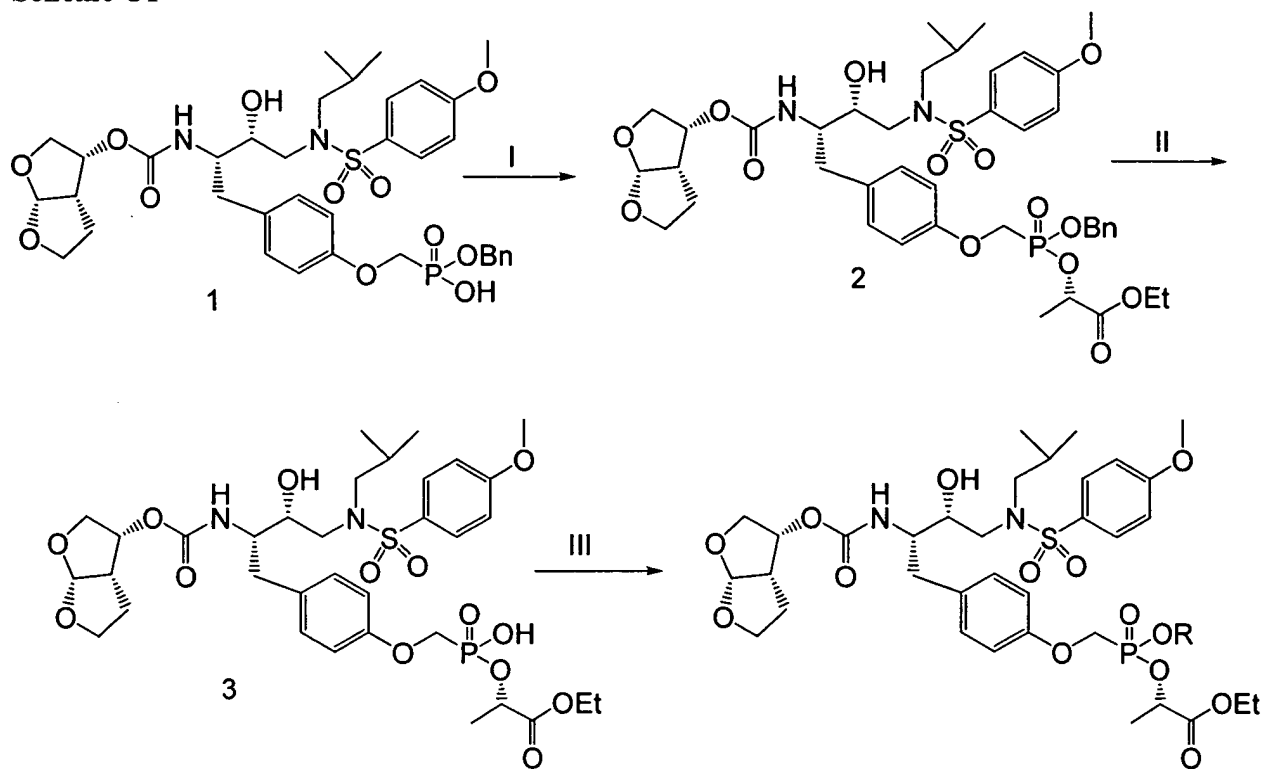
Oxime **4**: To a solution of aldehyde **3** (96 mg, 0.163 mmol) in 1,2-dichloroethane (0.65 mL) was added hydroxylamine **2** (72.5 mg, 0.244 mmol), triethylamine (22.7  $\mu$ L, 0.163 mmol) and  $\text{MgSO}_4$  (10 mg). The reaction mixture was stirred at room temperature for 2 hours then the mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NaCl, dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (90/10 – ethyl acetate/hexane) affording, GS-277771, oxime **4** (0.104 g, 85%) as a solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.13 (s, 1H), 7.72 (d, 2H), 7.51 (d, 2H), 7.27 (d, 2H), 7.00 (d, 2H), 5.67 (d, 1H), 5.02 (m, 2H), 4.54 (d, 2H), 4.21 (m, 4H), 3.92 (m, 1H), 3.89 (s, 3H), 3.88 (m, 1H), 3.97-3.71 (m, 2H), 3.85-3.70 (m, 2H), 3.16-2.99 (m, 2H), 3.16-2.81 (m, 7H), 1.84 (m, 1H), 1.64-1.48 (m, 2H), 1.37 (t, 6H), 0.94-0.90 (dd, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.0; MS (ESI) 756 (M+H).

### Scheme T1

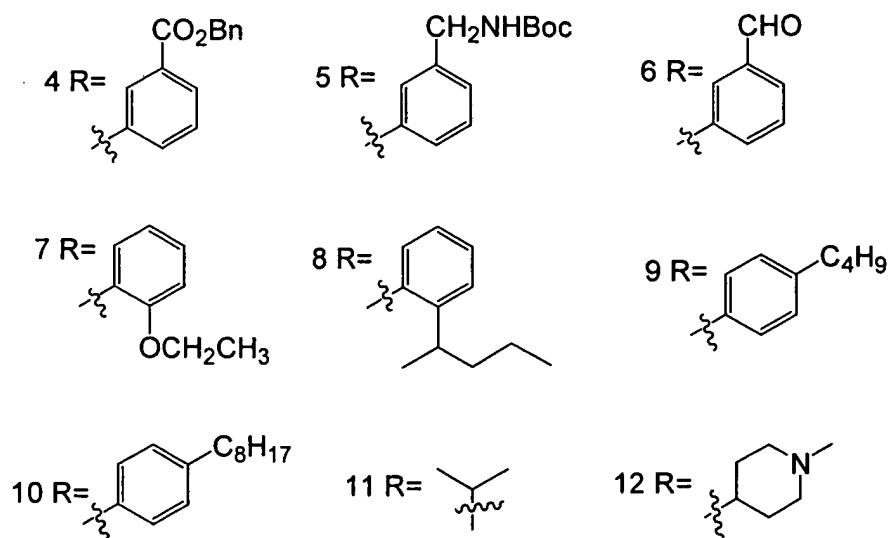


## Example Section U

Scheme U1



I. Ethyl(S)-(-)lactate/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/EtOAc; II.  $\text{H}_2$ /20%Pd-C/EtOAc-EtOH; III. ROH/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/EtOAc



#### Example U1

Compound 1 was prepared according to methods from previous Schemes.

#### Example U2

Compound 2: To a solution of compound 1 (5.50 g, 7.30 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (5.70g, 10.95 mmol), and Ethyl(S)-(-)lactate (1.30 g, 10.95 mmol) in DMF (50 mL) was added Diisopropylethylamine (5.08 mL, 29.2 mmol). The mixture was stirred for 7 hours after which was diluted in EtOAc. The organic phase was washed with H<sub>2</sub>O (5X), brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Isopropanol= 100/4) to give 3.45 g of compound 2.

#### Example U3

Compound 3: To the mixture of compound 2 (3.45 g) in EtOH/EtOAc (300 mL/100 mL) was added 20% Pd/C (0.700 g). The mixture was hydrogenated for 1 hour. Celite was added and the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and washed with ethanol. Concentration gave 2.61 g of compound 3.

#### Example U4

Compound 4: To a solution of compound 3 (1.00 g, 1.29 mmol) in dry dimethylformamide (5 mL) was added 3-Hydroxy-benzoic acid benzyl ester (0.589 g, 2.58 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.34 g, 2.58 mmol), followed by addition of Diisopropylethylamine (900  $\mu$ L, 5.16 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Isopropanol= 100/3) to provide 67.3 mg of compound 4: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.91 (2H, d, J=8.9 Hz), 7.75 (2H, m), 7.73-7.3 (13H, m), 7.25 (2H, m), 7.21-6.7 (6H, m), 5.87 (1H, m), 5.4-4.8 (6H, m), 4.78-4.21 (4H, m), 3.98 (3H, s), 2.1-1.75 (8H, m), 1.55 (3H, m), 1.28 (3H, m), 0.99 (6H, m).

#### Example U5

Compound 5: To a solution of compound 3 (1.40 g, 1.81 mmol) in dry dimethylformamide (5 mL) was added (4-Hydroxy-benzyl)-carbamic acid tert-butyl ester (0.80

g, 3.62 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.74 g, 3.62 mmol), followed by addition of Diisopropylethylamine (1.17 ml, 7.24 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{Isopropanol}$ = 100/3.5) to provide 770 mg of compound 5:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.8(2H, d,  $J$ =8.9Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-5.1(2H, m), 4.6-4.23 (4H,m), 3.98 (3H, s), 3.7-2.6 (15H, m), 2.2-1.8 (12H, m), 1.72 (3H, s), 1.58(3H, m), 1.25 (3H, m), 0.95 (6H, m).

#### Example U6

Compound 6: To a solution of compound 3 (1.00 g, 1.29 mmol) in dry dimethylformamide (6 mL) was added 3-Hydroxybenzaldehyde (0.320 g, 2.60 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.35 g, 2.60 mmol), followed by addition of Diisopropylethylamine (901  $\mu\text{L}$ , 5.16 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{Isopropanol}$ = 100/5) to provide 880 mg of compound 6.

#### Example U7

Compound 7: To a solution of compound 3 (150 mg, 0.190 mmol) in dry dimethylformamide (1 mL) was added 2-Ethoxy-phenol (48.0  $\mu\text{L}$ , 0.380 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (198 mg, 0.380 mmol), followed by addition of Diisopropylethylamine (132  $\mu\text{L}$ , 0.760 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{Isopropanol}$ = 100/4) to provide 84.7 mg of compound 7:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (2H, d,  $J$ =8.9 Hz), 7.15 (2H, m), 7.01-6.9 (8H, m), 5.66 (1H, m), 5.22-5.04 (2H, m), 4.56- 4.2 (6H, m), 4.08 (2H, m), 3.89 (3H, m), 3.85-3.69 (6H, m), 3.17-2.98 (7H, m), 2.80(3H, m) 1.86 (1H, m), 1.65(2H, m), , 1.62-1.22 (6H, m), 0.92(6H, m).

#### Example U8

Compound 8: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 2-(1-methylbutyl) phenol (21.2 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition of Diisopropylethylamine (45.0  $\mu$ L, 0.260 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 8.20 mg of compound 8:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (2H, d,  $J=8.9$  Hz), 7.25 (2H, m), 7.21-6.89 (8H, m), 5.7(1H, m), 5.29-4.9 (2H, m), 4.56- 4.2 (6H, m), 3.89 (3H, m), 3.85-3.69 (6H, m), 3.17-2.89 (8H, m), 2.85(3H, m), 2.3-1.65(4H, m), 1.55-1.35 (6H, m), 0.92(6H, m).

#### Example U9

Compound 9: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added) 4-N-Butylphenol (19.4 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition (45.0  $\mu$ L, 0.260 mmol) of Diisopropylethylamine. The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 9.61 mg of compound 9:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.8(2H, d,  $J=8.9$  Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-4.5 (4H, m), 4.3- 3.4.1 (4H, m), 3.9 (3H, m), 3.3- 2.59 (11H, m), 2.25 (2H, m), 1.85-1.5 (5H, m), 1.4-1.1(10H, m), 0.95(9H, m).

#### Example U10

Compound 10: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 4-Octylphenol (26.6 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition of Diisopropylethylamine (45.0  $\mu$ L, 0.260 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 7.70 mg of compound 10:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (2H, d,  $J=8.9$  Hz),

7.3 (2H, m), 7.2-6.8 (8H, m), 5.70 (1H, m), 5.3-4.9 (4H, m), 4.6- 3.9 (4H, m), 3.89 (3H, m), 3.85-2.59 (12H, m), 2.18-1.75 (10H, m), 1.69-1.50 (8H, m), 1.4-1.27(6H,m), 0.95(9H, m).

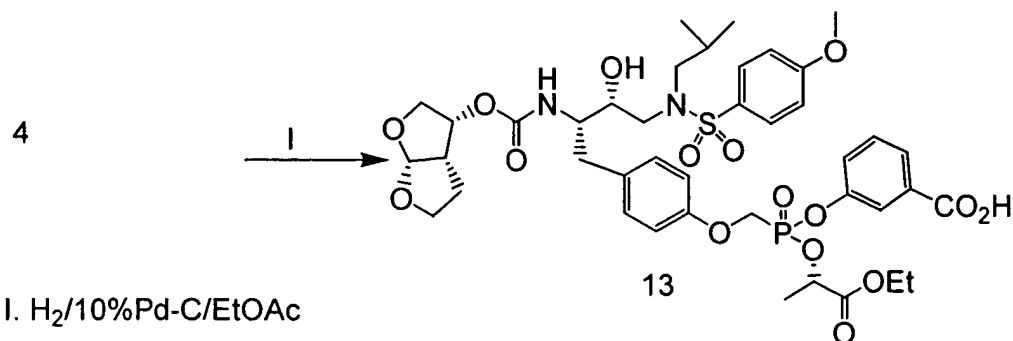
#### Example U11

Compound 11: To a solution of compound 3 (100 mg, 0.120 mmol) in dry dimethylformamide (1 mL) was added Isopropanol (20.0  $\mu$ L, 0.240 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (135 mg, 0.240 mmol), followed by addition of Diisopropylethylamine (83.0  $\mu$ L, 0.480 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2$ /Isopropanol= 100/4) to provide 12.2 mg of compound 11:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (2H, d,  $J=8.9$  Hz), 7.15 (2H, m), 7.0 (2H, m), 6.89 (2H, m), 5.65 (1H, m), 5.03-4.86(4H, m), 4.34-4.19 (3H, m), 3.89 (3H, s), 3.88 (1H, m), 3.82 (2H, m), 3.65 (4H, m), 3.2-2.9 (11H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

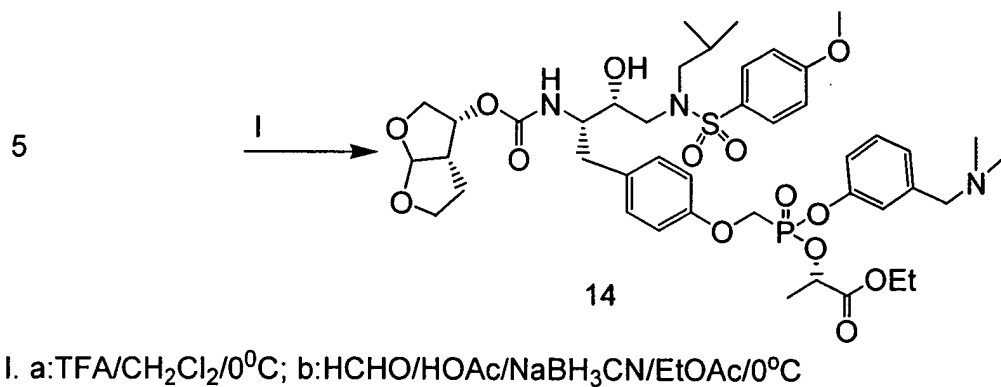
#### Example U12

Compound 12: To a solution of compound 3 (100 mg, 0.120 mmol) in dry dimethylformamide (1mL) was added 4-Hydroxy-1-methylpiperidine (30.0 mg, 0.240 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (135 mg, 0.240 mmol), followed by addition of Diisopropylethylamine (83.0  $\mu$ L, 0.480 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 50.1 mg of compound 12:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (2H, d,  $J=8.9$  Hz), 7.18 (2H, m), 7.0 (2H, m), 6.9 (2H, m), 5.67 (1H, m), 5.2-4.9 (4H, m), 4.30-4.11 (4H, m), 3.98 (1H, m), 3.89 (3H, s), 3.87 (1H, m), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (14H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

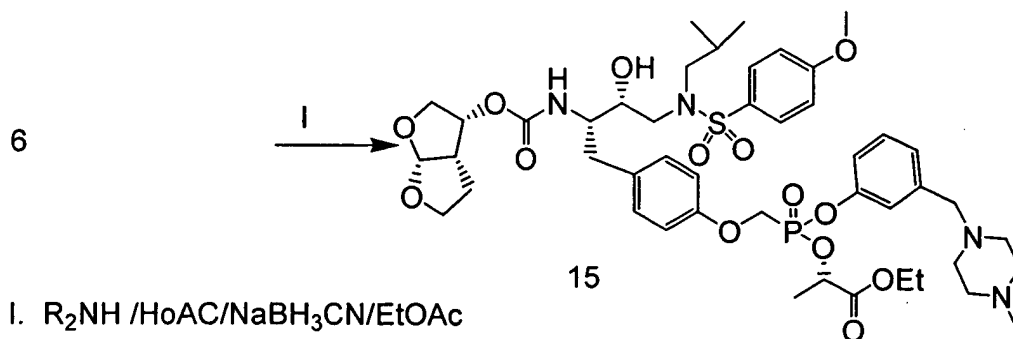
### Scheme U2



### Scheme U3



### Scheme U4



### Example U13

Compound 13: To a solution of compound 4 (4.9 g) in EtOAc (150ml) was added 20% Pd/C (0.90 g), the reaction mixture was hydrogenated for 1 hour. Celite was added and the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and washed with ethanol. Concentration gave 4.1 g of compound 13:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.91 (2H, d,  $J=8.9$

Hz), 7.75 (2H, m), 7.73-7.3 (8H, m), 7.25 (2H, m), 7.21-6.7(6H, m), 5.4-4.8(6H, m), 4.78-4.21 (4H, m), 3.98 (3H,s), 2.1-1.75 (8H, m), 1.55 (3H, m), 1.28(3H, m), 0.99(6H, m).

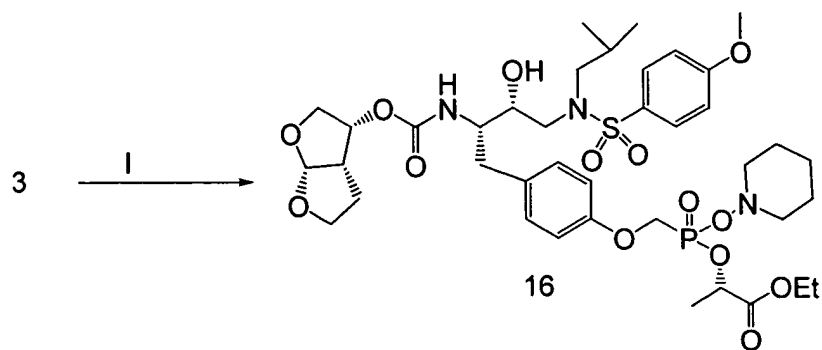
#### Example U14

Compound 14: To a solution of compound 5 (0.770 g, 0.790 mmol) in dichloromethane (10 mL), under ice-cooling, was added trifluoroacetic acid (5 mL), the resulting mixture was stirred at 25°C for two hours. The reaction mixture was concentrated under reduced pressure and the residue was co-evaporated with EtOAc to provide an yellow oil. To a solution of the above oil in (10 mL) of EtOAc, under ice-cooling and stirring was added formaldehyde (210  $\mu$ L, 2.86 mmol), acetic acid (252  $\mu$ L, 4.30 mmol), followed by sodium cyanoborohydride (178 mg, 2.86 mmol). The mixture was further stirred at 25°C for 2 hours. The above mixture was concentrated and diluted with EtOAc and washed with H<sub>2</sub>O (3X), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using reversed-phase HPLC to provide 420 mg of compound 14: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.8(2H, d, J=8.9Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-5.1(2H, m), 4.6-4.23 (4H,m), 3.98 (3H, s), 3.7-2.6 (15H, m), 2.2-1.8 (8H, m), 1.72 (3H, s), 1.58(3H, m), 1.25 (3H, m), 0.95 (6H, m).

#### Example U15

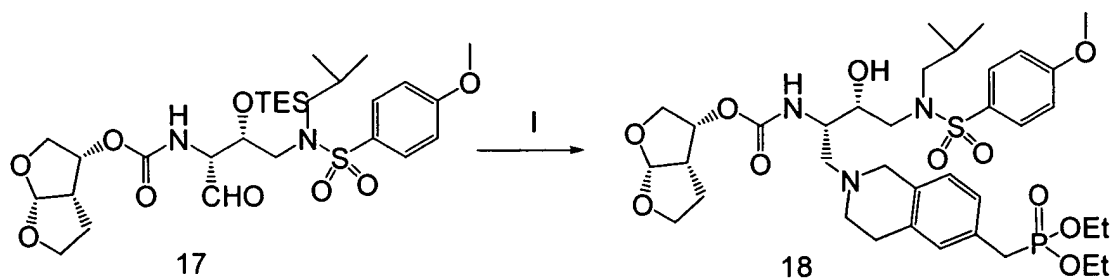
Compound 15: To a solution of compound 6 (100mg, 0.114 mmol) in EtOAc (1 mL) was added 1-Methyl-piperazine (63.2 mg, 0.570 mmol), acetic acid (34.0  $\mu$ l, 0.570 mmol) followed by Sodium Cyanoborohydride (14.3 mg, 0.228mmol). The mixture was stirred at 25°C for 14 hours. The reaction mixture was concentrated and diluted with EtOAc and washed with H<sub>2</sub>O (5X), brine (2x), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Isopropanol= 100/6.5) to give 5.22 mg of compound 15: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.73 (2H, d, J=8.9 Hz), 7.4-7.18(8H, m), 7.1-6.89 (2H, m), 5.67 (1H, m), 5.2-4.9 (4H, m), 4.30-4.11 (4H, m), 3.98 (1H, m), 3.89 (3H, s), 3.87 (1H, m), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (10H, m), 2.80-2.25 (8H,m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

## Scheme U5



I. Piperidin-1-ol/DCC/Pyridine

## Scheme U6



I. a:  $R_2NH$  /HOAc/ $NaBH_3CN$ /EtOAc b: 2%HF/ $CH_3CN$

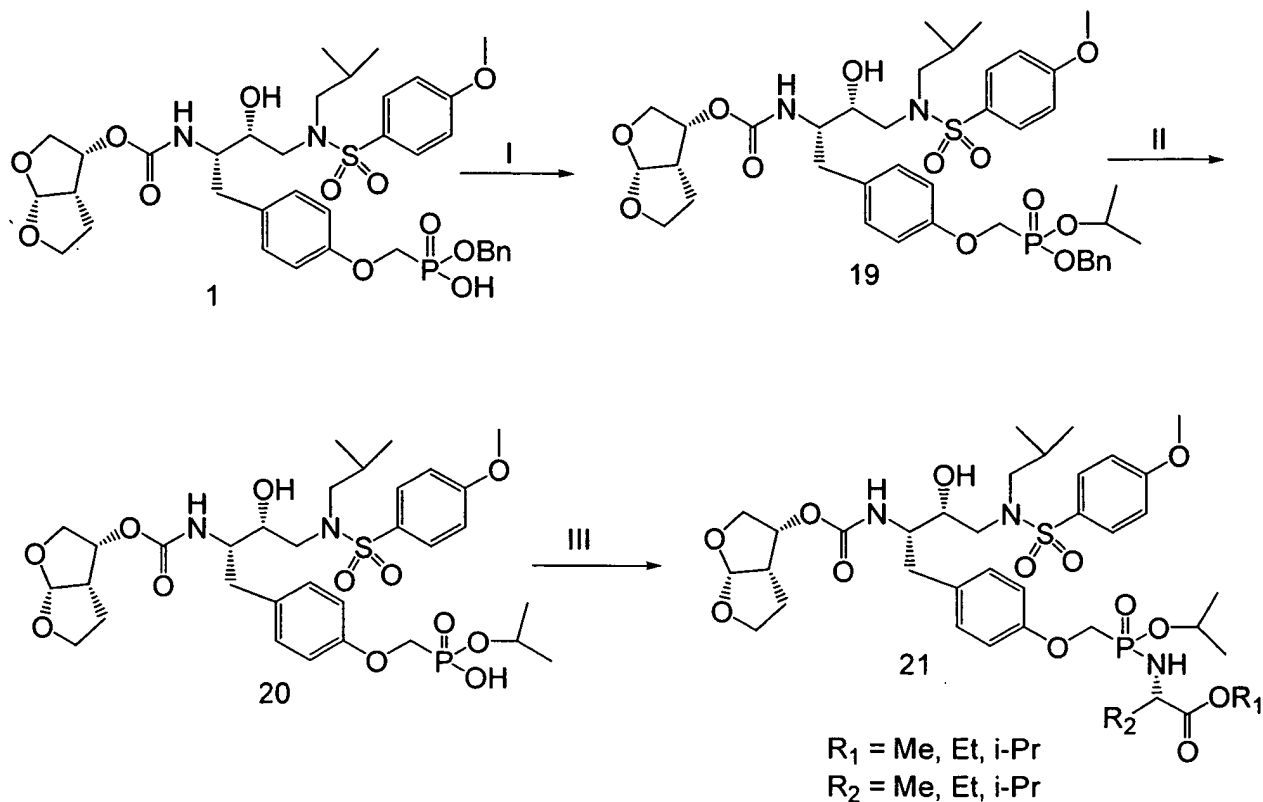
## Example U16

Compound 16: To a solution of compound 3 (100mg, 0.120 mmol) in Pyridine (600  $\mu$ L) was added Piperidin-1-ol (48.5 mg, 0.480 mmol), followed by N,N-Dicyclohexylcarbodiimide (99.0 mg, 0.480 mmol). The mixture was stirred for 6 hours, the solvent was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography ( $CH_2Cl_2$ /Methanol= 100/5) to provide 17 mg of compound 16:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.73 (2H, d,  $J=8.9$  Hz), 7.16 (2H, m), 7.0 (2H, m), 6.9 (2H, m), 5.68 (1H, m), 5.17 (1H, m), 5.04 (1H, m), 4.5-4.2 (4H, m), 3.90 (3H, s), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (10H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.5-1.27 (9H,m), 0.92(6H, m).

### Example U17

Compound 18: To a solution of compound 17 (148 mg, 0.240 mmol) in 4 mL of Methanol was added (1,2,3,4-Tetrahydro-isoquinolin-6-ylmethyl)-phosphonic acid diethyl ester (70.0 mg, 0.240 mmol), acetic acid (43.0  $\mu$ L, 0.720 mmol). The reaction mixture was stirred for 3 minutes, followed by addition of Sodium Cyanoborohydride (75.3 mg, 1.20 mmol). The reaction mixture was stirred at 25°C for 14 hours. The reaction mixture was diluted with EtOAc and washed with H<sub>2</sub>O (3X), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Isopropanol= 100/5) to give 59 mg of TES protected intermediate. 83  $\mu$ L of 48% HF solution was added to acetonitrile (4 mL) to prepare the 2% HF solution. The above 2% HF solution was added to TES protected intermediate (47 mg, 0.053 mmol) and the reaction mixture was stirred for 2 hours. The solvent was concentrated and the residue was diluted with EtOAc, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Methanol= 100/10) to give 35.2 mg of compound 18: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.73 (2H, d, J=8.9 Hz), 7.05 (2H, m), 6.89 (2H, m), 6.76 (1H, m), 5.75 (1H, m), 5.67 (1H, m), 5.3 (2H, m), 4.2-3.6 (12 H, m), 3.4-2.4 (11 H, m), 2.1-1.8 (6H, m), 1.4-1.28 ( 8 H, m), 0.92(6H, m).

# Scheme U7

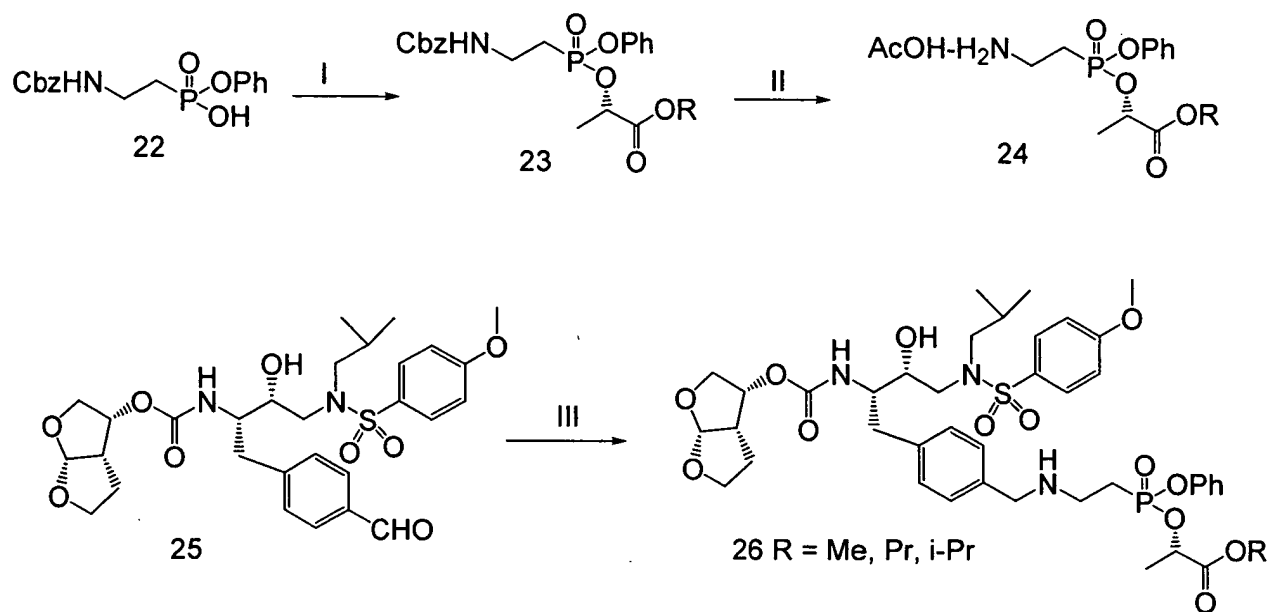


- I. Isopropanol/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/DMF;
- II.  $\text{H}_2$ /10%Pd-C/EtOAc-EtOH;
- III.  $\text{RNH}_2$ /Aldrithiol-2/ $\text{PPh}_3$ / $\text{iPr}_2\text{NEt}$ /pyridine

Compound 19 is prepared following the procedure for compound 2 by using monoacid 1.

Compound 20 is made following a hydrogenation of compound 19. Mono acid 20 reacts with corresponding amino esters in the presence of Aldrithiol-2 and triphenylphosphine to form compound 21.

# Scheme U8

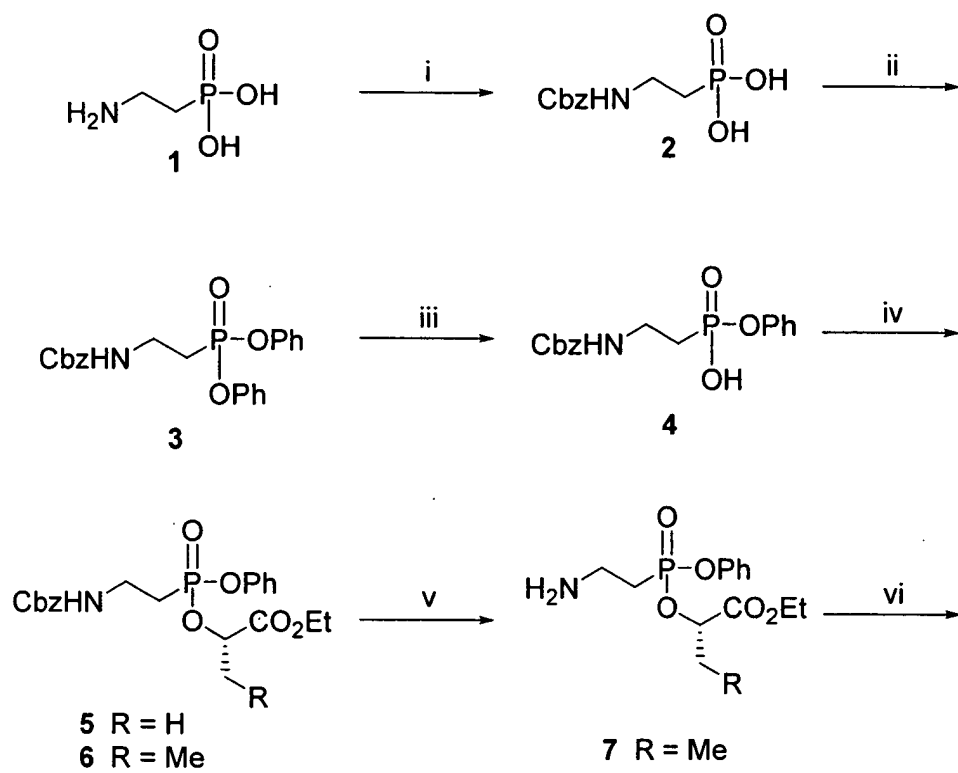


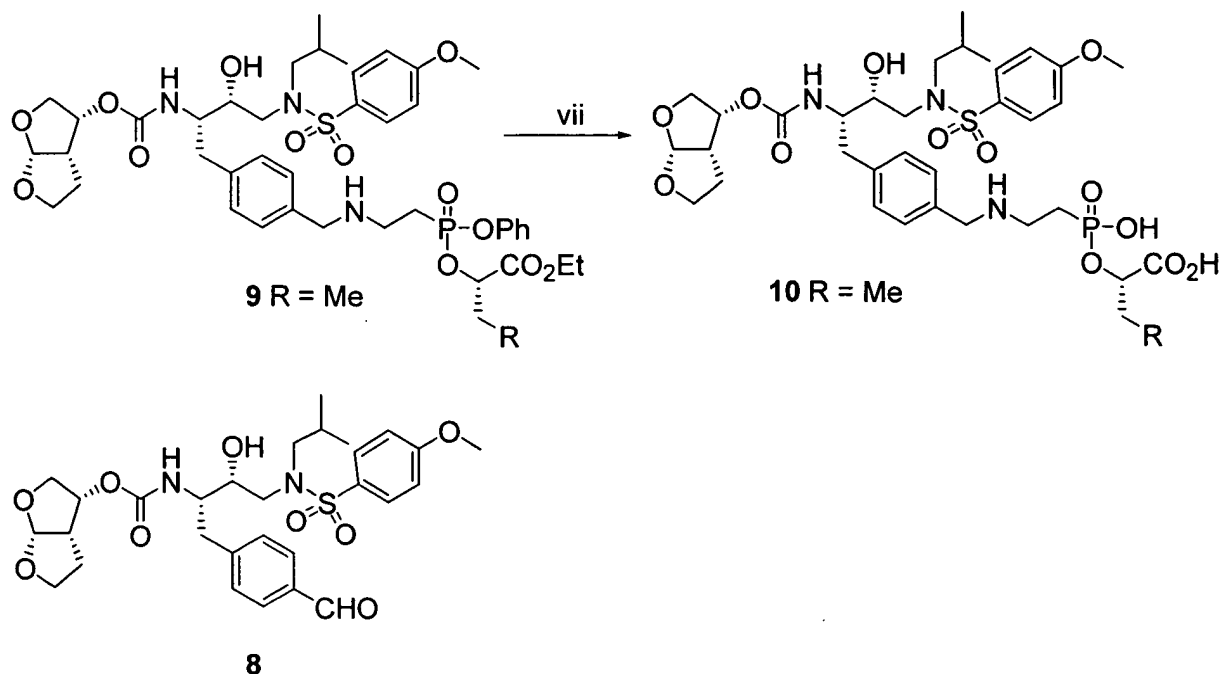
I. a. SOCl<sub>2</sub>/60 °C; b. Alkyl (s)-lactate/Et<sub>3</sub>N; II. H<sub>2</sub>/10%Pd-C/EtOAc-HOAc;  
 III. a. compound 25/MgSO<sub>4</sub>; b. HOAc/NaBH<sub>3</sub>CN

Monoacid 22 is treated with thionyl chloride at 60°C to form monochloridate, which reacts with corresponding alkyl (s)-lactate to generate monolactate 23. Monolactate 23 is hydrogenated with 10%Pd-C in the presence of acetic acid to form amine 24. Aldehyde 25 reacts with amine 24 in the presence of MgSO<sub>4</sub> to form the intermediate imine, which is reduced with sodium cyanoborohydride to afford compound 26.

## Example Section V

Scheme V1





**Reagents and conditions:** i. CbzCl, NaOH, tol/H<sub>2</sub>O, 100%; ii. a. SOCl<sub>2</sub>, DMF, tol, 65°C; b. PhOH, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 71%; iii. aq. NaOH, CH<sub>3</sub>CN, 79%; iv. a. SOCl<sub>2</sub>, DMF, tol, 65°C; b. ethyl lactate, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, (**5**) 85%; 2-hydroxy butyric acid ethyl ester, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, (**6**) 75%; v. H<sub>2</sub>, AcOH, 10% Pd/C, EtOH, 94%; vi. a. **7** + **8**, 1,2-DCE, MgSO<sub>4</sub>; b. NaBH<sub>3</sub>CN, AcOH, 50%; vii. pig liver esterase, 20% DMSO/PBS, 40°C, 25%.

### Example V1

Compound 2: A 3L, 3-neck flask was equipped with a mechanical stirrer and addition funnel and charged with 2-aminoethyl phosphonic acid (60.0g, 480 mmol). 2N Sodium hydroxide (480 mL, 960 mmol) was added and flask cooled to 0°C. Benzyl chloroformate (102.4 g, 600 mmol) in toluene (160mL) was added dropwise with vigorous stirring. The reaction mixture was stirred at 0°C for 30 minutes, then at room temperature for 4 h. 2N sodium hydroxide (240 mL, 480 mmol) was added, followed by benzyl chloroformate (20.5 g, 120 mmol) and the reaction mixture was vigorously stirred for 12 h. The reaction mixture was washed with diethyl ether (3x). The aqueous layer was acidified to pH 2 with concentrated HCl to give a white precipitate. Ethyl acetate was added to the mixture and concentrated HCl (80 mL, 960 mmol) was added. The aqueous layer was extracted with ethyl acetate and combined organic layer was dried (MgSO<sub>4</sub>) and concentrated to give a waxy, white solid (124 g, 479 mmol, 100%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.45-7.30 (m, 5 H, Ar), 5.06 (d, *J* = 14.7 Hz, 2

H,  $\text{CH}_2\text{Ph}$ ), 3.44-3.31 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.03-1.91 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{P}$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  26.3.

#### Example V2

Compound 3: To a mixture of compound 2 (50.0 g, 193 mmol) in toluene (1.0 L) was added DMF (1.0 mL) followed by thionyl chloride (56 mL, 768 mmol). The reaction mixture was heated at  $65^\circ\text{C}$  for 3-4 h under a stream of argon. The reaction mixture was cooled to room temperature and concentrated. Residual solvent was removed under high vacuum for 1 h. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (1.0 L) and cooled to  $0^\circ\text{C}$ . Triethylamine (161 mL, 1158 mmol) was added, followed by phenol (54.5 g, 579 mmol). The reaction mixture was warmed to room temperature overnight, then washed with 1.0N HCl, saturated  $\text{NaHCO}_3$  solution, brine and dried ( $\text{MgSO}_4$ ). Concentrated and purified (silica gel, 1:1 EtOAc/Hex) to give a pale yellow solid (56 g, 136 mmol, 71%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40-7.10 (m, 15 H, Ar), 5.53 (br s, 1 H, NH), 5.11 (br s, 2 H,  $\text{CH}_2\text{Ph}$ ), 3.72-3.60 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.49-2.30 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{P}$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.9.

#### Example V3

Compound 4: To a solution of compound 3 (64 g, 155.6 mmol) in acetonitrile (500 mL) at  $0^\circ\text{C}$  was added 2.0M sodium hydroxide. The reaction mixture was stirred at  $0^\circ\text{C}$  for 30 min, then at room temperature for 2.5 h. The reaction mixture was concentrated to 100 mL and diluted with  $\text{H}_2\text{O}$  (500 mL). The aqueous solution was washed with EtOAc (3 x 300 mL). The aqueous layer was acidified to pH 1 with concentrated HCl, producing a white precipitate. The mixture was extracted with EtOAc (4 x 300 mL) and combined organic layer was washed with brine and dried ( $\text{MgSO}_4$ ). Concentration gave a solid, which was recrystallized from hot EtOAc (450 mL) to give a white solid (41.04 g, 122 mmol, 79%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.45-7.10 (m, 10 H, Ar), 5.09 (s, 2 H,  $\text{CH}_2\text{Ph}$ ), 3.53-3.30 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.25-2.10 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{P}$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  24.5.

#### Example V4

Compound 5: To a mixture of compound 4 (28 g, 83 mmol) in toluene (500 mL) was added DMF (1.0 mL), followed by thionyl chloride (36.4 mL, 499 mmol). The mixture was heated at  $65^\circ\text{C}$  for 2 h providing a pale yellow solution. The reaction mixture was concentrated

and dried for 45 min under high vacuum. The residue was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (350 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (45.3 mL, 332 mmol) was added slowly, followed by the dropwise addition of ethyl lactate (18.8 mL, 166 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 30 min, then warmed to room temperature overnight. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with 1 N HCl, saturated  $\text{NaHCO}_3$  solution, brine and dried ( $\text{MgSO}_4$ ).

Concentration and purification (silica gel, 1:5 to 1:0 EtOAc/Hex) gave a pale yellow oil (30.7 g, 71 mmol, 85%) as a mixture of diastereomers which were separated by HPLC (Dynamax reverse phase C-18 column, 60% acetonitrile/ $\text{H}_2\text{O}$ ). More polar diastereomer:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40-7.10 (m, 10 H, Ar), 5.65 (s, 1 H, NH), 5.12 (s, 2 H,  $\text{CH}_2\text{Ph}$ ), 5.10-5.00 (m, 1 H, OCHC) 4.17 (q,  $J = 6.9$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 3.62 (dt,  $J_1 = 20.4$  Hz,  $J_2 = 6.0$  Hz, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.25 (dt,  $J_1 = 18.0$  Hz,  $J_2 = 6.0$  Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{P}$ ), 1.60 (dd,  $J_1 = J_2 = 6.9$  Hz, 3 H,  $\text{CHCH}_3$ ), 1.23 (t,  $J = 6.9$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  26.2. Less polar diastereomer:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40-7.10 (m, 10 H, Ar), 5.87 (s, 1 H, NH), 5.13 (s, 2 H,  $\text{CH}_2\text{Ph}$ ), 5.10-5.00 (dq,  $J_1 = J_2 = 6.9$  Hz, 1 H, OCHC) 4.22 (q,  $J = 7.2$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 3.68 (dt,  $J_1 = 21.6$  Hz,  $J_2 = 6.9$  Hz, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.40-2.20 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{P}$ ), 1.49 (dd,  $J_1 = 70.2$  Hz,  $J_2 = 6.9$  Hz, 3 H,  $\text{CHCH}_3$ ), 1.28 (t,  $J = 6.9$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.3.

#### Example V5

Compound 6: 2-Hydroxy-butyric acid ethyl ester was prepared as follows: To a solution of L-2-aminobutyric acid (100g, 970 mmol) in 1.0 N  $\text{H}_2\text{SO}_4$  (2 L) at  $0^\circ\text{C}$  was added  $\text{NaNO}_2$  (111 g, 1610 mmol) in  $\text{H}_2\text{O}$  (400 mL) over 2 h. The reaction mixture was stirred at room temperature for 18h. Reaction mixture was extracted with EtOAc (4x) and combined organic layer was dried ( $\text{MgSO}_4$ ) and concentrated to give a yellow solid (41.5 g). This solid was dissolved in absolute ethanol (500 mL) and concentrated HCl (3.27 mL, 39.9 mmol) was added. Reaction mixture was heated to  $80^\circ\text{C}$ . After 24 h, concentrated HCl (3 mL) was added and reaction continued for 24 h. Reaction mixture was concentrated and product was distilled to give a colorless oil (31 g, 235 mmol, 59%).

To a mixture of compound 4 (0.22 g, 0.63 mmol) in anhydrous acetonitrile (3.0 mL) was added thionyl chloride (0.184 mL, 2.52 mmol). The mixture was heated at  $65^\circ\text{C}$  for 1.5 h providing a pale yellow solution. The reaction mixture was concentrated and dried for 45 min

under high vacuum. The residue was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (3.3 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.26 mL, 1.89 mmol) was added slowly, followed by the dropwise addition of 2-hydroxy-butyric acid ethyl ester (0.167 mL, 1.26 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 5 min, then warmed to room temperature overnight. The reaction mixture was concentrated, dissolved in EtOAc and washed with 1.0 N HCl, saturated  $\text{NaHCO}_3$  solution, brine and dried ( $\text{MgSO}_4$ ). Concentration and purification (silica gel, 3:2 EtOAc/Hex) gave a pale yellow oil (0.21 g, 0.47 mmol, 75%). For major diastereomer,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35-7.10 (m, 10 H, Ar), 5.91 (s, 1 H, NH), 5.12 (s, 2 H,  $\text{CH}_2\text{Ph}$ ), 4.94-4.83 (m, 1 H, OCHC), 4.27-4.12 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 3.80-3.50 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.39-2.19 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{P}$ ), 1.82-1.71 (m, 2 H,  $\text{CHCH}_2\text{CH}_3$ ), 1.30-1.195 (m, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 0.81 (t,  $J = 7.5$  Hz, 3 H,  $\text{CHCH}_2\text{CH}_3$ );  $^{31}\text{P}$  NMR (120 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.3. For minor diastereomer,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35-7.10 (m, 10 H, Ar), 5.74 (s, 1 H, NH), 5.11 (s, 2 H,  $\text{CH}_2\text{Ph}$ ), 4.98-4.94 (m, 1 H, OCHC), 4.27-4.12 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 3.80-3.50 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.39-2.19 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{P}$ ), 1.98-1.82 (m, 2 H,  $\text{CHCH}_2\text{CH}_3$ ), 1.30-1.195 (m, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.00 (t,  $J = 7.5$  Hz, 3 H,  $\text{CHCH}_2\text{CH}_3$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  26.2.

#### Example V6

Compound 7: A mixture of compound 6, (0.53 g, 1.18 mmol) acetic acid (0.135 mL, 2.36 mmol) and 10% palladium on activated carbon (0.08 g) in absolute ethanol (12 mL) was stirred under a hydrogen atmosphere (1 atm) for 3 h. Reaction mixture was filtered through Celite, concentrated, and resubjected to identical reaction conditions. After 2 h, Celite was added to the reaction mixture and mixture was stirred for 2 min, then filtered through a pad of Celite and concentrated. Dried under high vacuum to give the diastereomeric acetate salt as a oil (0.42 g, 1.11 mmol, 94%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40-7.10 (m, 5 H, Ar), 5.00-4.80 (m, 1 H, OCHC), 4.28-4.10 (m, 2 H,  $\text{OCH}_2\text{CH}_2$ ), 3.32-3.14 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 2.45-2.22 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{P}$ ), 1.97 (s, 3 H, Ac), 1.97-1.70 (m, 2 H,  $\text{CHCH}_2\text{CH}_3$ ), 1.30-1.18 (m, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.00 (t,  $J = 7.5$  Hz, 1 H,  $\text{CHCH}_2\text{CH}_3$ ), 0.80 (t,  $J = 7.5$  Hz, 2 H,  $\text{CHCH}_2\text{CH}_3$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  27.6 (major, 1.85), 26.0 (minor, 1.01).

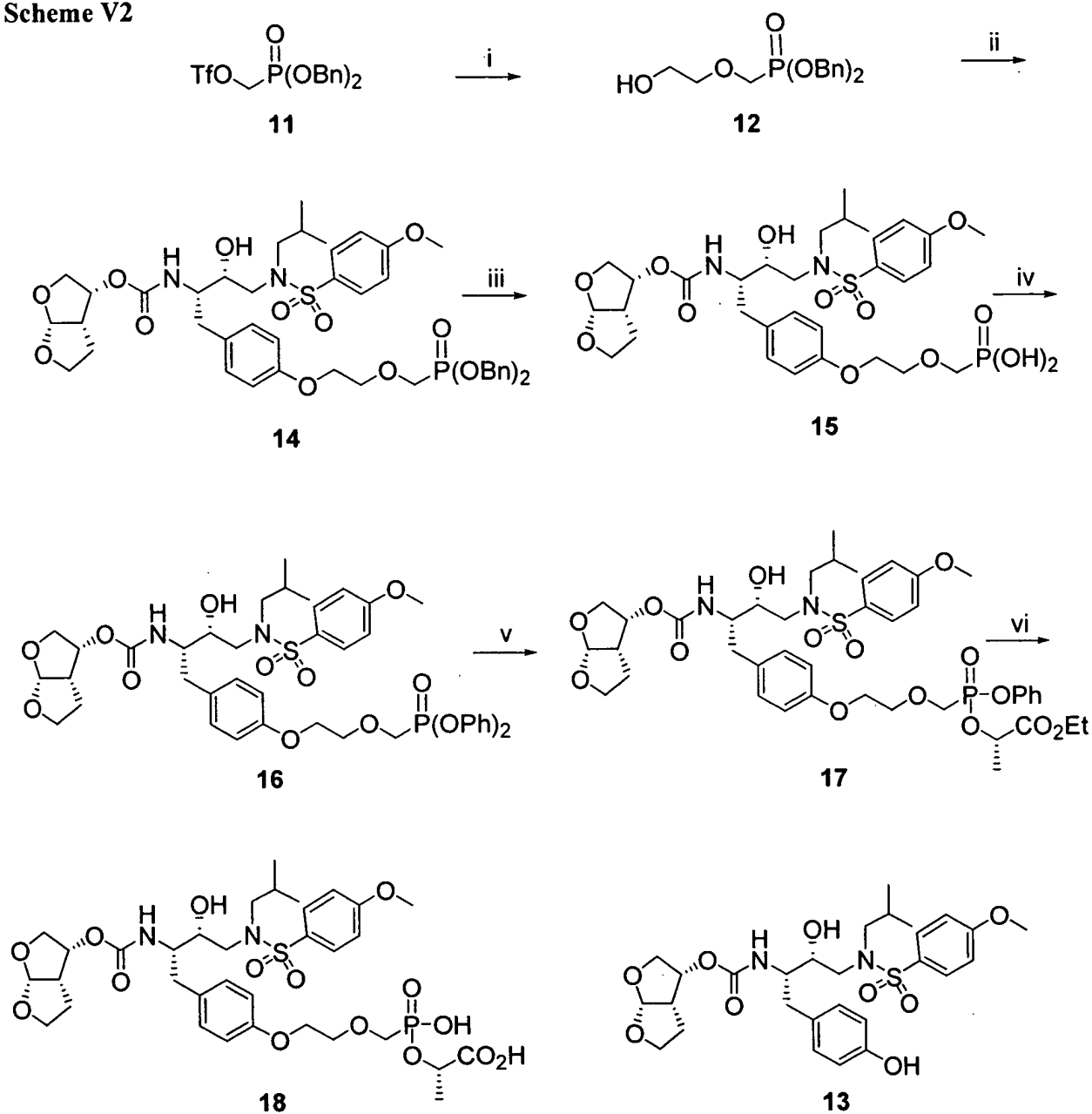
### Example V7

Compound 9: A solution of aldehyde **8** (0.596 g, 1.01 mmol) and compound **7** (0.42 g, 1.11 mmol) were stirred together in 1,2-dichloroethane (4.0 mL) in the presence of  $\text{MgSO}_4$  for 3 h. Acetic acid (0.231 mL, 4.04 mmol) and sodium cyanoborohydride (0.127 g, 2.02 mmol) were added and reaction mixture was stirred for 50 min at room temperature. Reaction mixture was quenched with saturated  $\text{NaHCO}_3$  solution, diluted with EtOAc, and vigorously stirred for 5 min. Brine was added and extracted with EtOAc (2x). Combined organic layer was dried ( $\text{MgSO}_4$ ) concentrated and purified (silica gel, EtOAc, then 10% EtOH/EtOAc) to give a colorless foam. Acetonitrile (4 mL) and trifluoroacetic acid (0.06 mL) were added and concentrated to a volume of 1 mL.  $\text{H}_2\text{O}$  (10 mL) was added and lyophilized to give the TFA salt as a white powder (0.51 g, 0.508 mmol, 50%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  7.79 (d,  $J = 8.4$  Hz, 2 H,  $(\text{SO}_2\text{C}(\text{CH})_2$ ), 7.43-7.20 (m, 9 H, Ar), 7.10 (d,  $J = 8.4$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_3$ ), 5.85 (d,  $J = 8.4$  Hz, 1 H, NH), 5.55 (d,  $J = 4.5$  Hz, 1 H, OCHO), 5.00-4.75 (m, 2 H,  $\text{CH}_2\text{CHOC}(\text{O})$ , POCHC), 4.39-4.05 (m, 2 H,  $\text{PhCH}_2\text{N}$ ,  $\text{OCH}_2\text{CH}_3$ ), 3.89 (s, 3 H,  $\text{OCH}_3$ ), 3.88-3.30 (m, 9H), 3.15-2.84 (m, 5 H), 2.65-2.42 (m, 3 H), 2.10-1.68 (m, 5 H), 1.65-1.15 (m, 5 H), 1.05-0.79 (m, 9 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  24.8 (major, 1.85), 23.1 (minor, 1.01).

### Example V8

Compound 10: Compound **9** (0.041 g, 0.041 mmol) was dissolved in DMSO (1.9 mL) and to this solution was added phosphate buffered saline, pH 7.4 (10 mL) and pig liver esterase (Sigma, 0.2 mL). Reaction mixture was stirred for 24 h at  $40^\circ\text{C}$ . After 24 h, additional esterase (0.2 mL) was added and reaction was continued for 24 h. Reaction mixture was concentrated, resuspended in methanol and filtered. Filtrate was concentrated and purified by reverse phase chromatography to give a white powder after lyophilization (8 mg, 0.010 mmol, 25%).  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.78 (d,  $J = 8.9$  Hz, 2 H,  $(\text{SO}_2\text{C}(\text{CH})_2$ ), 7.43-7.35 (m, 4 H, Ar), 7.11 (d,  $J = 8.9$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_3$ ), 5.62 (d,  $J = 5.2$  Hz, 1 H, OCHO), 4.96-4.77 (m, 2 H,  $\text{CH}_2\text{CHOC}(\text{O})$ , POCHC), 4.21 (br s, 2 H,  $\text{PhCH}_2\text{N}$ ), 3.97-3.70 (m, 6 H), 3.90 (s, 3 H,  $\text{OCH}_3$ ), 3.50-3.30 (m, 3 H), 3.26-3.02 (m, 2 H), 2.94-2.58 (m, 4 H), 2.09-1.78 (m, 5 H), 1.63-1.52 (m, 2 H), 1.05-0.97 (m, 3 H); 0.94 (d,  $J = 6.7$  Hz, 3 H), 0.88 (d,  $J = 6.7$  Hz, 3 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  20.8.

Scheme V2



### Example V9

Compound 12: To a solution of compound **11** (4.10 g, 9.66 mmol) and anhydrous ethylene glycol (5.39 mL, 96.6 mmol) in anhydrous DMF (30 mL) at 0°C was added powdered magnesium *tert*-butoxide (2.05 g, 12.02 mmol). The reaction mixture was stirred at 0°C for 1.5 h, then concentrated. The residue was partitioned between EtOAc and H<sub>2</sub>O and washed with 1 N HCl, saturated NaHCO<sub>3</sub> solution, and brine. Organic layer dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a colorless oil (1.55 g, 48%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.37 (s, 10 H, Ar), 5.40-5.05 (m, 4 H, CH<sub>2</sub>Ph), 3.84 (d, *J* = 8.1 Hz, 2 H, PCH<sub>2</sub>O), 3.70-3.60 (m, 4 H, OCH<sub>2</sub>CH<sub>2</sub>O, OCH<sub>2</sub>CH<sub>2</sub>O); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 22.7.

### Example V10

Compound 14: To a solution of compound **12** (0.75 g, 2.23 mmol) and 2,6-lutidine (0.78 mL, 6.69 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at -78°C was added trifluoromethanesulfonic anhydride (0.45 mL, 2.68 mmol). The reaction mixture was stirred at -78°C for 40 min, then diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 1 N HCl, saturated NaHCO<sub>3</sub> and dried (MgSO<sub>4</sub>). Concentration gave a yellow oil that was dissolved in anhydrous acetonitrile (20 mL). Phenol **13** (1.00 g, 1.73 mmol) was added to the solution, which was cooled to 0°C. Cesium carbonate (0.619 g, 1.90 mmol) was added and reaction mixture was stirred at 0°C for 2 h, then at room temperature for 1.5 h. Additional cesium carbonate (0.200 g, 0.61 mmol) was added and reaction was continued for 1.5 h, then filtered. Concentration of the filtrate and purification (silica gel, 3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave a yellow gum (1.005 g, 65%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.71 (d, *J* = 8.7 Hz, 2 H, SO<sub>2</sub>C(CH)<sub>2</sub>), 7.34 (s, 10 H, PhCH<sub>2</sub>O), 7.11 (d, *J* = 8.1 Hz, 2 H, CH<sub>2</sub>C(CH)<sub>2</sub>(CH)<sub>2</sub>), 6.98 (d, *J* = 8.7 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>3</sub>), 6.78 (d, *J* = 8.7 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>2</sub>), 5.62 (d, *J* = 5.4 Hz, 1 H, OCHO), 5.16-4.97 (m, 6 H), 4.05-3.65 (m, 12 H), 3.86 (s, 3 H, OCH<sub>3</sub>), 3.19-2.66 (m, 7 H), 1.95-1.46 (m, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.88 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 21.9.

### Example V11

Compound 15: A mixture of compound **14** (0.410 g, 0.457 mmol) and 10% palladium on carbon (0.066 g) in ethanol (5.0 mL) was stirred under a hydrogen atmosphere (1 atm) for 16 h. Celite was added and the mixture was stirred for 5 min, then filtered through Celite and

concentrated to give a foam (0.350 g, 107%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.76 (d,  $J = 8.7$  Hz, 2 H,  $\text{SO}_2\text{C}(\text{CH})_2$ ), 7.15 (d,  $J = 8.4$  Hz, 2 H,  $\text{CH}_2\text{C}(\text{CH})_2(\text{CH})_2$ ), 7.08 (d,  $J = 8.4$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_3$ ), 6.82 (d,  $J = 8.4$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_2$ ), 5.59 (d,  $J = 5.4$  Hz, 1 H,  $\text{OCHO}$ ), 5.16-4.97 (masked by  $\text{CD}_3\text{OH}$ , 1 H), 4.09-4.02 (m, 2 H), 3.99-3.82 (m, 10 H), 3.88 (s, 3 H,  $\text{OCH}_3$ ), 3.52-3.32 (m, 1 H), 3.21-2.75 (m, 5 H), 2.55-2.40 (m, 1 H), 2.10-1.95 (m, 1 H), 1.75-1.25 (m, 2 H), 0.93 (d,  $J = 6.3$  Hz, 3 H,  $\text{CH}(\text{CH}_3)_2$ ), 0.88 (d,  $J = 6.6$  Hz, 3 H,  $\text{CH}(\text{CH}_3)_2$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  19.5.

#### Example V12

Compound 16: Compound **15** (0.350 g, 0.488 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL), each time filling with  $\text{N}_2$ . Residue was dissolved in anhydrous pyridine (2.5 mL) and phenol (0.459 g, 4.88 mmol) was added. This solution was heated to  $70^\circ\text{C}$ , then 1,3-dicyclohexylcarbodiimide (0.403 g, 1.93 mmol) was added and reaction mixture was heated at  $70^\circ\text{C}$  for 7 h. Reaction mixture was concentrated, coevaporated with toluene and residue obtained was diluted with EtOAc, precipitating 1,3-dicyclohexylurea. The mixture was filtered and filtrate concentrated and residue obtained was purified (silica gel, 2% MeOH/ $\text{CH}_2\text{Cl}_2$ , then another column 75% EtOAc/Hex) to give a clear oil (0.1324 g, 31%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.71 (d,  $J = 8.7$  Hz, 2 H,  $\text{SO}_2\text{C}(\text{CH})_2$ ), 7.41-7.18 (m, 10 H, Ar), 7.14 (d,  $J = 8.4$  Hz, 2 H,  $\text{CH}_2\text{C}(\text{CH})_2(\text{CH})_2$ ), 6.99 (d,  $J = 9.0$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_3$ ), 6.83 (d,  $J = 8.4$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_2$ ), 5.64 (d,  $J = 5.1$  Hz, 1 H,  $\text{OCHO}$ ), 5.16-4.92 (m, 2 H), 4.32-3.62 (m, 12 H), 3.87 (s, 3 H,  $\text{OCH}_3$ ), 3.22-2.73 (m, 7 H), 1.95-1.75 (m, 3 H), 0.93 (d,  $J = 6.6$  Hz, 3 H,  $\text{CH}(\text{CH}_3)_2$ ), 0.88 (d,  $J = 6.6$  Hz, 3 H,  $\text{CH}(\text{CH}_3)_2$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.3.

#### Example V13

Compound 17: To a solution of compound **16** (0.132 g, 0.152 mmol) in acetonitrile (1.5 mL) at  $0^\circ\text{C}$  was added 1.0 M NaOH (0.38 mL, 0.381 mmol). Reaction mixture was stirred for 2 h at  $0^\circ\text{C}$ , then Dowex 50 ( $\text{H}^+$ ) resin was added until pH = 1. The resin was removed by filtration and the filtrate was concentrated and washed with EtOAc/Hex (1:2, 25 mL), then dried under high vacuum to give a clear film (0.103 g, 85%). This film was coevaporated with anhydrous pyridine (3 x 5 mL), filling with  $\text{N}_2$ . The residue was dissolved in anhydrous pyridine (1 mL) and ethyl lactate (0.15 mL, 1.30 mmol) was added and reaction mixture was heated at  $70^\circ\text{C}$ .

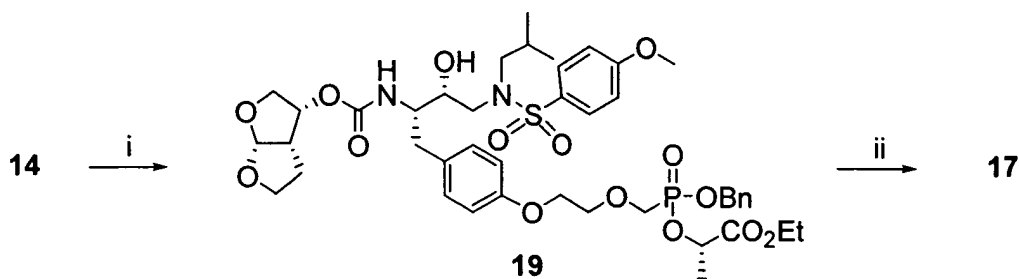
After 5 min, 1,3-dicyclohexylcarbodiimide (0.107 g, 0.520 mmol) was added and reaction mixture was stirred at 70°C for 2.5 h. Additional 1,3-dicyclohexylcarbodiimide (0.055 g, 0.270 mmol) was added and reaction continued for another 1.5 h. Reaction mixture was concentrated and coevaporated with toluene and diluted with EtOAc, precipitating 1,3-dicyclohexylurea. The mixture was filtered and filtrate concentrated and residue obtained was purified (silica gel, 80 to 100% EtOAc/Hex) to give a white foam (0.0607 g, 52%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.71 (d, *J* = 8.7 Hz, 2 H, SO<sub>2</sub>C(CH)<sub>2</sub>), 7.39-7.16 (m, 5 H, Ar), 7.13 (d, *J* = 8.1 Hz, 2 H, CH<sub>2</sub>C(CH)<sub>2</sub>(CH)<sub>2</sub>), 6.99 (d, *J* = 9.0 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>3</sub>), 6.82 (d, *J* = 8.4 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>2</sub>), 5.64 (d, *J* = 5.1 Hz, 1 H, OCHO), 5.16-4.92 (m, 3 H), 4.35-3.65 (m, 14 H), 3.87 (s, 3 H, OCH<sub>3</sub>), 3.22-2.73 (m, 7 H), 1.95-1.80 (m, 3 H), 1.59 (d, *J* = 6.9 Hz, 1.5 H, CCHCH<sub>3</sub>), 1.47 (d, *J* = 7.2 Hz, 1.5 H, CCHCH<sub>3</sub>), 1.37-1.18 (m, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.88 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 19.2, 17.2.

#### Example V14

Compound 18: Compound 17 (11.5 mg, 0.013 mmol) was dissolved in DMSO (0.14 mL) and acetonitrile (0.29 mL). PBS (pH 7.4, 1.43 mL) was added slowly with stirring. Porcine liver esterase (Sigma, 0.1 mL) was added and reaction mixture was gently stirred at 38°C. After 24 h, additional porcine liver esterase (0.1 mL) and DMSO (0.14 mL) were added and reaction mixture stirred for 48 h at 38°C. Reaction mixture concentrated and methanol was added to precipitate the enzyme. The mixture was filtered, concentrated and purified by reverse phase chromatography to give a white powder after lyophilization (7.1 mg, 69%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.76 (d, *J* = 8.7 Hz, 2 H, SO<sub>2</sub>C(CH)<sub>2</sub>), 7.15 (d, *J* = 8.4 Hz, 2 H, CH<sub>2</sub>C(CH)<sub>2</sub>(CH)<sub>2</sub>), 7.08 (d, *J* = 9.0 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>3</sub>), 6.83 (d, *J* = 8.7 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>2</sub>), 5.59 (d, *J* = 5.1 Hz, 1 H, OCHO), 5.16-4.90 (masked by CD<sub>3</sub>OH, 2 H), 4.19-3.65 (m, 12 H), 3.88 (s, 3 H, OCH<sub>3</sub>), 3.50-3.27 (m, 1 H), 3.20-2.78 (m, 5 H), 2.55-2.40 (m, 1 H), 2.05-1.90 (m, 1 H), 1.75-1.30 (m, 2 H), 1.53 (d, *J* = 6.6 Hz, 3 H, CCHCH<sub>3</sub>), 0.93 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.88 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>31</sup>P NMR (121 MHz, CD<sub>3</sub>OD): δ 16.7.

Alternatively, compound 17 was prepared as described below (Scheme V3).

### Scheme V3



#### Example V15

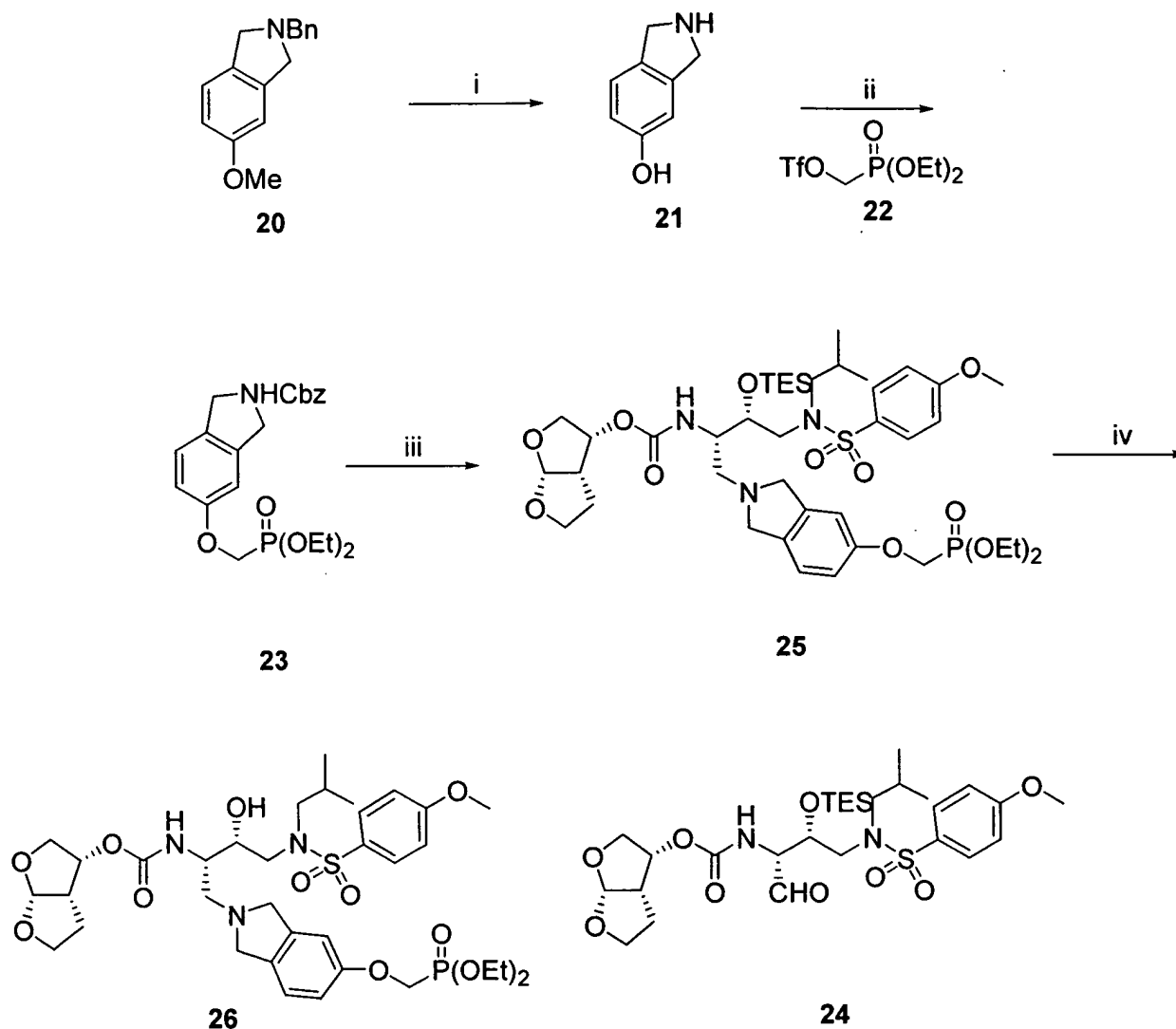
Compound 19: To a solution of compound **14** (0.945 g, 1.05 mmol) in anhydrous toluene (10.0 mL) was added 1,4-diazobicyclo[2.2.2] octane (0.130 g, 1.16 mmol) and reaction mixture was refluxed for 2 h. After cooling to room temperature, reaction mixture was diluted with EtOAc and washed with 1.0 N HCl and dried (MgSO<sub>4</sub>). Concentration gave a white foam (0.785 g, 93%). Residue was dissolved in anhydrous DMF (10.0 mL) and to this solution was added ethyl (S)-lactate (0.23 mL, 2.00 mmol) and diisopropylethylamine (0.70 mL, 4.00 mmol), followed by benzotriazol-1-yloxytripyrroldinophosphonium hexafluorophosphate (1.041 g, 2.00 mmol). Reaction mixture was stirred for 20 h, then concentrated and residue was dissolved in EtOAc and washed with 1.0 N HCl, saturated NaHCO<sub>3</sub>, brine and dried (MgSO<sub>4</sub>). Concentration and purification (silica gel, 2 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave an off-white foam (0.520 g, 59%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.72 (d, *J* = 7.5 Hz, 2 H, SO<sub>2</sub>C(CH)<sub>2</sub>), 7.50-7.27 (m, 4 H, Ar), 7.12 (d, *J* = 8.1 Hz, 2 H, CH<sub>2</sub>C(CH)<sub>2</sub>(CH)<sub>2</sub>), 7.00 (d, *J* = 6.6 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>3</sub>), 6.81 (d, *J* = 8.4 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>2</sub>), 5.64 (d, *J* = 5.1 Hz, 1 H, OCHO), 5.37-4.90 (m, 5 H), 4.35-3.65 (m, 14 H), 3.88 (s, 3 H, OCH<sub>3</sub>), 3.24-2.70 (m, 7 H), 1.90-1.70 (m, 3 H), 1.54 (d, *J* = 6.9 Hz, 1.5 H, CCHCH<sub>3</sub>), 1.47 (d, *J* = 6.9 Hz, 1.5 H, CCHCH<sub>3</sub>), 1.37-1.22 (m, 3 H), 0.93 (d, *J* = 6.3 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.89 (d, *J* = 6.0 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 22.3, 21.2.

#### Example V16

Compound 17: A mixture of compound **19** (0.520 g, 0.573 mmol) and 10% palladium on carbon (0.055 g) in ethanol (10 mL) was stirred under a hydrogen atmosphere (1 atm) for 2 h. Celite was added to the reaction mixture and stirred for 5 min, then mixture was filtered through Celite and concentrated to give a white foam (0.4649 g, 99%). Residue was dissolved in

anhydrous DMF (5.0 mL) and to this solution was added phenol (0.097 g, 1.03 mmol), diisopropylethylamine (0.36 mL, 2.06 mmol) followed by benzotriazol-1-yloxytripyrroldinophosphonium hexafluorophosphate (0.536 g, 1.03 mmol). Reaction mixture was stirred for 20 h, then concentrated and residue was dissolved in EtOAc and washed with 1 N HCl, H<sub>2</sub>O, sat. NaHCO<sub>3</sub>, brine and dried (MgSO<sub>4</sub>). Concentration and purification (silica gel, 2 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave a white foam (0.180 g, 35%).

## Scheme V4



Reagents and conditions: i. a. 48% HBr, 120°C, 65%; b. H<sub>2</sub>, Pd(OH)<sub>2</sub>, EtOH, 100%;  
 ii. CbzCl, NaOH, toluene/H<sub>2</sub>O, 0°C to rt, 43%; b. **22**, CsCO<sub>3</sub>, CH<sub>3</sub>CN, 99%;  
 iii. a. H<sub>2</sub>, Pd/C, AcOH, EtOAc/EtOH, 95%; b. **24**, NaBH(OAc)<sub>3</sub>, 1,2-DCE, 21%;  
 iv, 4% HF/CH<sub>3</sub>CN, 62%.

## Example V17

Compound **21**: Compound **20** (11.5 g, 48.1 mmol) in 48% HBr (150 mL) was heated at 120°C for 4 h, then cooled to room temperature and diluted with EtOAc. Mixture was neutralized with saturated NaHCO<sub>3</sub> solution and solid NaHCO<sub>3</sub> and extracted with EtOAc

containing MeOH. Organic layer dried (MgSO<sub>4</sub>), concentrated, and purified (silica gel, 1:2 EtOAc/Hex with 1% MeOH) to give a brown solid (7.0 g, 65%). The resulting compound (7.0 g, 31.1 mmol) and 10% palladium hydroxide (2.1 g) in EtOH (310 mL) was stirred under a hydrogen atmosphere for 1 d, then filtered through Celite and concentrated to give an off-white solid (4.42 g, 100%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.01 (d, *J* = 7.8 Hz, 1 H, Ar), 6.64 (s, 1 H, Ar), 6.61 (d, *J* = 8.1 Hz, 2 H, Ar), 4.07 (s, 2 H, ArCH<sub>2</sub>N), 4.05 (s, 2 H, ArCH<sub>2</sub>N).

#### Example V18

Compound 22: To a solution of compound **21** (4.42 g, 32.7 mmol) in 1.0 M NaOH (98 mL, 98.25 mmol) at 0°C was added dropwise benzyl chloroformate (7.00 mL, 49.13 mmol) in toluene (7 mL). After addition was complete, reaction mixture was stirred overnight at room temperature. Reaction mixture was diluted with EtOAc and extracted with EtOAc (3x). Combined organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a white solid (3.786 g, 43%). The resulting compound (0.6546 g, 2.43 mmol) was dissolved in anhydrous acetonitrile (10 mL), and compound **23** (0.782 g, 2.92 mmol) was added, followed by cesium carbonate (1.583 g, 4.86 mmol). Reaction mixture was stirred for 2 h at room temperature, then filtered, concentrated, and purified (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a brownish oil (1.01 g, 99%).

#### Example V19

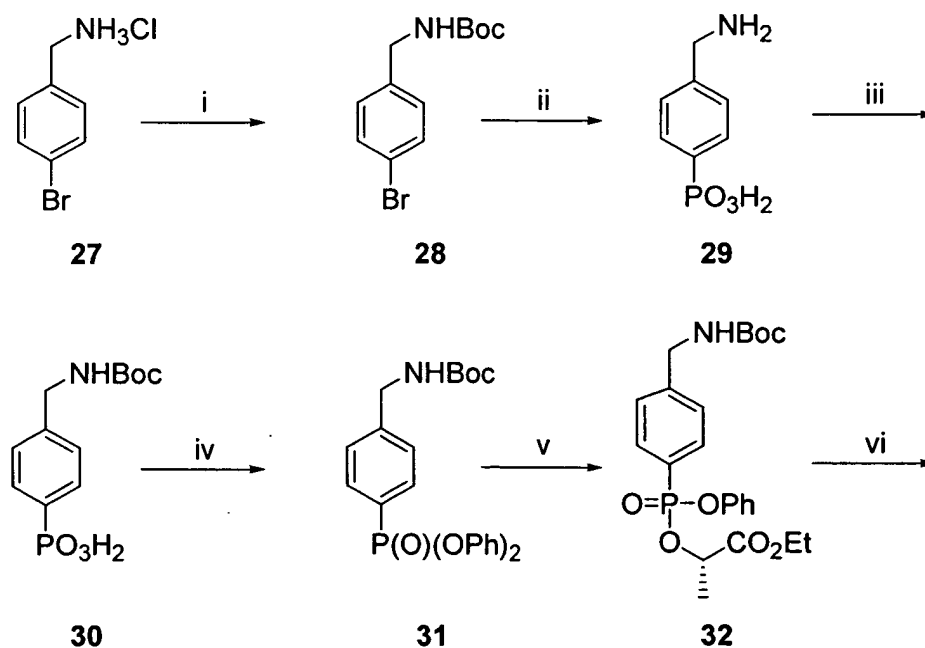
Compound 25: To a solution of compound **22** (0.100 g, 0.238 mmol) in EtOAc/EtOH (2 mL, 1:1) was added acetic acid (14 μL, 0.238 mmol) and 10% palladium on carbon (0.020 g) and the mixture was stirred under a hydrogen atmosphere for 2 h. Celite was added to the reaction mixture and stirred for 5 min, then filtered through Celite. Concentration and drying under high vacuum gave a reddish film (0.0777 g, 95%). The resulting amine (0.0777 g, 0.225 mmol) and aldehyde **24** (0.126 g, 0.205 mmol) in 1,2-dichloroethane (1.2 mL) were stirred for 5 min at 0°C, then sodium triacetoxyborohydride (0.0608 g, 0.287 mmol) was added. Reaction mixture was stirred for 1 h at 0°C, then quenched with saturated NaHCO<sub>3</sub> solution and brine. Extracted with EtOAc, the organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a brown foam (38.7 mg, 21%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.74 (d, *J* = 8.7 Hz, 2 H, Ar), 7.09 (d, *J* = 8.7 Hz, 1 H, Ar), 7.05-6.72 (m, 4 H, Ar), 5.71 (d, *J* = 5.1 Hz, 1 H), 5.22-5.07 (m, 2 H), 4.22-4.17 (m, 7 H), 4.16-3.69 (m, 9 H), 3.82 (s, 3 H), 3.25-2.51 (m, 7 H),

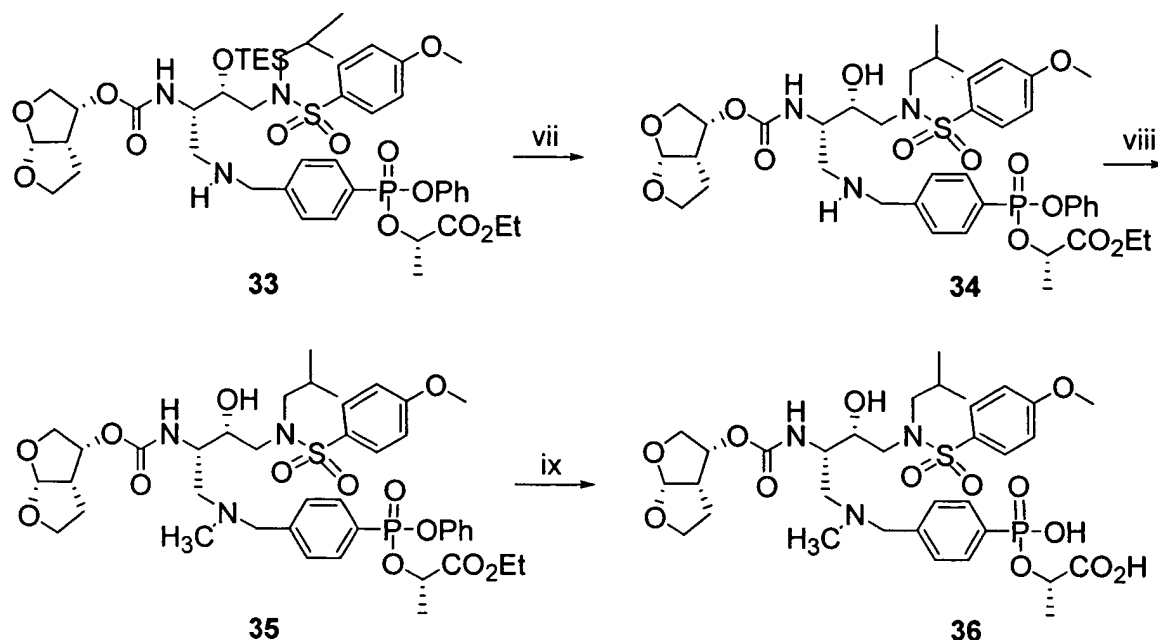
2.22-1.70 (m, 3 H), 1.37 (t,  $J = 6.9$  Hz, 6 H), 1.10-0.58 (m, 21 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.5.

#### Example V20

Compound 26: To a solution of compound **25** (38.7 mg, 0.0438 mmol) in acetonitrile (0.5 mL) at  $0^\circ\text{C}$  was added 48% HF (0.02 mL). The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated  $\text{NaHCO}_3$  solution and extracted with EtOAc. Organic layer was separated, dried ( $\text{MgSO}_4$ ), concentrated and purified (silica gel, 3 to 5%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) to give a red film (21.2 mg, 62%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.73 (d,  $J = 8.7$  Hz, 2 H, Ar), 7.10 (d,  $J = 8.7$  Hz, 1 H, Ar), 6.97 (d,  $J = 8.70$  Hz, 2 H), 6.90-6.76 (m, 2 H), 5.72 (d,  $J = 5.1$  Hz, 1 H), 5.41 (d,  $J = 9.0$  Hz, 1 H), 5.15 (q,  $J = 6.6$  Hz, 1 H), 4.38-4.17 (m, 7 H), 4.16-3.65 (m, 9 H), 3.87 (s, 3 H), 3.20-2.82 (m, 7 H), 2.75-1.79 (m, 3 H), 1.37 (t,  $J = 6.9$  Hz, 6 H), 0.90 (d,  $J = 6.6$  Hz, 3 H), 0.88 (d,  $J = 6.6$  Hz, 3 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.3.

#### Scheme V5





Reagents and conditions: i.  $\text{Boc}_2\text{O}$ , NaOH,  $\text{H}_2\text{O}$ , 96%;  
 ii. a.  $\text{HP}(\text{OEt})_2$ ,  $\text{Et}_3\text{N}$ ,  $(\text{PPh}_3)_4\text{Pd}$ ,  $90^\circ\text{C}$ , b.  $\text{TMSBr}$ ,  $\text{CH}_3\text{CN}$ , 65%;  
 iii.  $\text{Boc}_2\text{O}$ , NaOH,  $\text{THF}/\text{H}_2\text{O}$ , 89%; iv.  $\text{PhOH}$ , DCC, pyr,  $70^\circ\text{C}$ , 71%;  
 v. a. NaOH,  $\text{CH}_3\text{CN}$ , 94%; b. Et lactate, DCC, pyr,  $70^\circ\text{C}$ , 80%; vi. a. TFA,  $\text{CH}_2\text{Cl}_2$ ;  
 b. **24**, AcOH,  $\text{NaBH}_3\text{CN}$ , EtOH, 33%; vii. 4%  $\text{HF}/\text{CH}_3\text{CN}$ , 88%;  
 viii. HCHO, AcOH,  $\text{NaBH}_3\text{CN}$ , EtOH, 67%;  
 ix.  $\text{CH}_3\text{CN}$ , DMSO, PBS, porcine liver esterase,  $38^\circ\text{C}$ , 21%.

### Example V21

**Compound 28:** To a mixture of 4-bromobenzylamine hydrochloride (15.23 g, 68.4 mmol) in  $\text{H}_2\text{O}$  (300 mL) was added sodium hydroxide (8.21 g, 205.2 mmol), followed by di-*tert*-butyl dicarbonate (16.45g, 75.3 mmol). Reaction mixture was vigorously stirred for 18 h, then diluted with EtOAc (500 mL). Organic layer separated and aqueous layer extracted with EtOAc (200 mL). Combined organic layer was dried ( $\text{MgSO}_4$ ), concentrated and dried under high vacuum to give a white solid (18.7 g, 96%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41 (d,  $J = 8.4$  Hz, 2 H), 7.12 (d,  $J = 8.3$  Hz, 2 H), 4.82 (s, 1 H, NH), 4.22 (d,  $J = 6.1$  Hz, 2 H), 1.41 (s, 9 H).

#### Example V22

Compound 29: Compound **28** (5.00 g, 17.47 mmol) was coevaporated with toluene. Diethyl phosphite (11.3 mL, 87.36 mmol) was added and mixture was coevaporated with toluene (2x). Triethylamine (24.0 mL, 174.7 mmol) was added and mixture was purged with argon for 10 min, then tetrakis(triphenylphosphine) palladium(0) (4.00 g, 3.49 mmol) was added. Reaction mixture was refluxed for 18 h, cooled, concentrated and diluted with EtOAc. Washed with 0.5 N HCl, 0.5 M NaOH, H<sub>2</sub>O, brine and dried (MgSO<sub>4</sub>). Concentrated and purification (silica gel, 70% EtOAc/Hex) gave an impure reaction product as a yellow oil (6.0 g). This material (6.0 g) was dissolved in anhydrous acetonitrile (30 mL) and cooled to 0°C. Bromotrimethylsilane (11.5 mL, 87.4 mmol) was added and reaction mixture was warmed to room temperature over 15 h. Reaction mixture was concentrated, dissolved in MeOH (50 mL) and stirred for 1.5 h. H<sub>2</sub>O (1 mL) was added and mixture stirred for 2 h. Concentrated to dryness and dried under high vacuum, then triturated with Et<sub>2</sub>O containing 2% MeOH to give a white solid (3.06 g, 65 %). <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): δ 7.67 (dd, *J* = 12.9, 7.6 Hz, 2 H), 7.45-7.35 (m, 2 H), 4.10 (s, 2 H); <sup>31</sup>P NMR (121 MHz, D<sub>2</sub>O): δ 12.1.

#### Example V23

Compound 30: Compound **29** (4.78 g, 17.84 mmol) was dissolved in H<sub>2</sub>O (95 mL) containing sodium hydroxide (3.57 g, 89.20 mmol). Di-*tert*-butyl dicarbonate (7.63 g, 34.94 mmol) was added, followed by THF (25 mL). The clear reaction mixture was stirred overnight at room temperature then concentrated to ~100 mL. Washed with EtOAc and acidified to pH 1 with 1 N HCl and extracted with EtOAc (7x). Combined organic layer was dried (MgSO<sub>4</sub>), concentrated and dried under high vacuum. Trituration with Et<sub>2</sub>O gave a white powder (4.56 g, 89%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.85-7.71 (m, 2 H), 7.39-7.30 (m, 2 H), 4.26 (s, 2 H), 1.46 (s, 9 H); <sup>31</sup>P NMR (121 MHz, CD<sub>3</sub>OD): δ 16.3.

#### Example V24

Compound 31: Compound **30** (2.96 g, 10.32 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL). To this residue was added phenol (9.71 g, 103.2 mmol) and mixture was coevaporated with anhydrous pyridine (2 x 10 mL). Pyridine (50 mL) was added and solution heated to 70°C. After 5 min, 1,3-dicyclohexylcarbodiimide (8.51 g, 41.26 mmol) was added and resulting mixture was stirred for 8 h at 70°C. Reaction mixture was cooled and concentrated and

coevaporated with toluene. Residue obtained was diluted with EtOAc and the resulting precipitate was removed by filtration. The filtrate was concentrated and purified (silica gel, 20 to 40% EtOAc/Hex, another column 30 to 40% EtOAc/Hex) to give a white solid (3.20 g, 71%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.90 (dd,  $J = 13.8, 8.2$  Hz, 2 H), 7.41-7.10 (m, 14 H), 5.17 (br s, 1 H, NH), 4.35 (d,  $J = 5.2$  Hz, 2 H), 1.46 (s, 9 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.8.

#### Example V25

Compound 32: To a solution of compound **31** (3.73 g, 8.49 mmol) in acetonitrile (85 mL) at  $0^\circ\text{C}$  was added 1 M NaOH (21.2 mL, 21.21 mmol). Reaction mixture was stirred at  $0^\circ\text{C}$  for 30 min, then warmed to room temperature over 4 h. Reaction mixture cooled to  $0^\circ\text{C}$  and Dowex ( $\text{H}^+$ ) residue was added to pH 2. Mixture was filtered, concentrated and residue obtained was triturated with EtOAc/Hex (1:2) to give a white powder (2.889 g, 94%). This compound (2.00 g, 5.50 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL). The residue was dissolved in anhydrous pyridine (30 mL) and ethyl (S)-lactate (6.24 mL, 55 mmol) and reaction mixture was heated to  $70^\circ\text{C}$ . After 5 min, 1,3-dicyclocarbodiimide (4.54 g, 22.0 mmol) was added. Reaction mixture was stirred at  $70^\circ\text{C}$  for 5 h, then cooled and concentrated. Residue was dissolved in EtOAc and precipitate was removed by filtration. The filtrate was concentrated and purified (25 to 35% EtOAc/Hex, another column 40% EtOAc/Hex) to give a colorless oil (2.02 g, 80%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96-7.85 (m, 2 H), 7.42-7.35 (m, 2 H), 7.35-7.08 (m, 4 H), 5.16-5.00 (m, 1 H), 4.93 (s, 1 H, NH), 4.37 (d,  $J = 5.5$  Hz, 1 H), 4.21 (q,  $J = 7.3$  Hz, 1 H), 4.11 (dq,  $J = 5.7, 2.2$  Hz, 1 H), 1.62-1.47 (m, 3 H), 1.47 (s, 9 H), 1.27 (t,  $J = 7.3$  Hz, 1.5 H), 1.17 (t,  $J = 7.3$  Hz, 1.5 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.1, 15.0.

#### Example V26

Compound 33: Compound **32** (2.02 g, 4.36 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (41 mL) and cooled to  $0^\circ\text{C}$ . To this solution was added trifluoroacetic acid (3.5 mL) and reaction mixture was stirred at  $0^\circ\text{C}$  for 1 h, then at room temperature for 3 h. Reaction mixture was concentrated, coevaporated with EtOAc and diluted with  $\text{H}_2\text{O}$  (400 mL). Mixture was neutralized with Amberlite IRA-67 weakly basic resin, then filtered and concentrated. Coevaporation with MeOH and dried under high vacuum to give the TFA amine salt as a semi-solid (1.48 g, 94%). To a solution of the amine (1.48 g, 4.07 mmol) in absolute ethanol (20 mL) at  $0^\circ\text{C}$  was added

aldehyde **24** (1.39 g, 2.26 mmol), followed by acetic acid (0.14 mL, 2.49 mmol). After stirring for 5 min, sodium cyanoborohydride (0.284 g, 4.52 mmol) was added and reaction mixture stirred for 30 min at 0°C. Reaction was quenched with saturated NaHCO<sub>3</sub> solution and diluted with EtOAc and H<sub>2</sub>O. Aqueous layer was extracted with EtOAc (3x) and combined organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 2 to 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give white foam (0.727 g, 33%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.98-7.86 (m, 2 H), 7.71 (d, *J* = 8.6 Hz, 2 H), 7.49 (br s, 2 H), 7.38-7.05 (m, 5 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 5.72 (d, *J* = 5.1 Hz, 1 H), 5.28-5.00 (m, 2 H), 4.30-3.72 (m, 12 H), 3.42-3.58 (m, 1 H), 3.20-2.68 (m, 7 H), 2.25-1.42 (m, 6 H), 1.26 (t, *J* = 7.2 Hz, 1.5 H), 1.17 (t, *J* = 7.2 Hz, 1.5 H), 1.08-0.50 (m, 21 H); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 16.1, 15.1.

#### Example V27

Compound **34**: To a solution of compound **33** (0.727 g, 0.756 mmol) in acetonitrile (7.6 mL) at 0°C was added 48% hydrofluoric acid (0.152 mL) and reaction mixture was stirred for 40 min at 0°C, then diluted with EtOAc and H<sub>2</sub>O. Saturated NaHCO<sub>3</sub> was added and aqueous layer was extracted with EtOAc (2x). Combined organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 4 to 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a colorless foam (0.5655 g, 88%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.95-7.82 (m, 2 H), 7.67 (d, *J* = 8.1 Hz, 2 H), 7.41 (br s, 2 H), 7.38-7.05 (m, 5 H), 6.95 (d, *J* = 7.2 Hz, 2 H), 5.76 (d, *J* = 7.9 Hz, 1 H), 5.67 (d, *J* = 5.0 Hz, 1 H), 5.32-4.98 (m, 2 H), 4.25-3.75 (m, 13 H), 3.25-2.70 (m, 7 H), 2.15-1.76 (m, 3 H), 1.53-1.41 (m, 3 H), 1.25-1.08 (m, 3 H), 0.87 (d, *J* = 4.2 Hz, 6 H); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 16.1, 15.0.

#### Example V28

Compound **35**: To a solution of compound **33** (0.560 g, 0.660 mmol) in absolute ethanol (13 mL) at 0°C was added 37% formaldehyde (0.54 mL, 6.60 mmol), followed by acetic acid (0.378 mL, 6.60 mmol). The reaction mixture was stirred at 0°C for 5 min, then sodium cyanoborohydride (0.415 g, 6.60 mmol) was added. Reaction mixture was warmed to room temperature over 2 h, then quenched with saturated NaHCO<sub>3</sub> solution. EtOAc was added and mixture was washed with brine. Aqueous layer was extracted with EtOAc (2x) and combined organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a white foam (0.384 g, 67%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.95-7.82 (m, 2 H), 7.71 (d, *J*

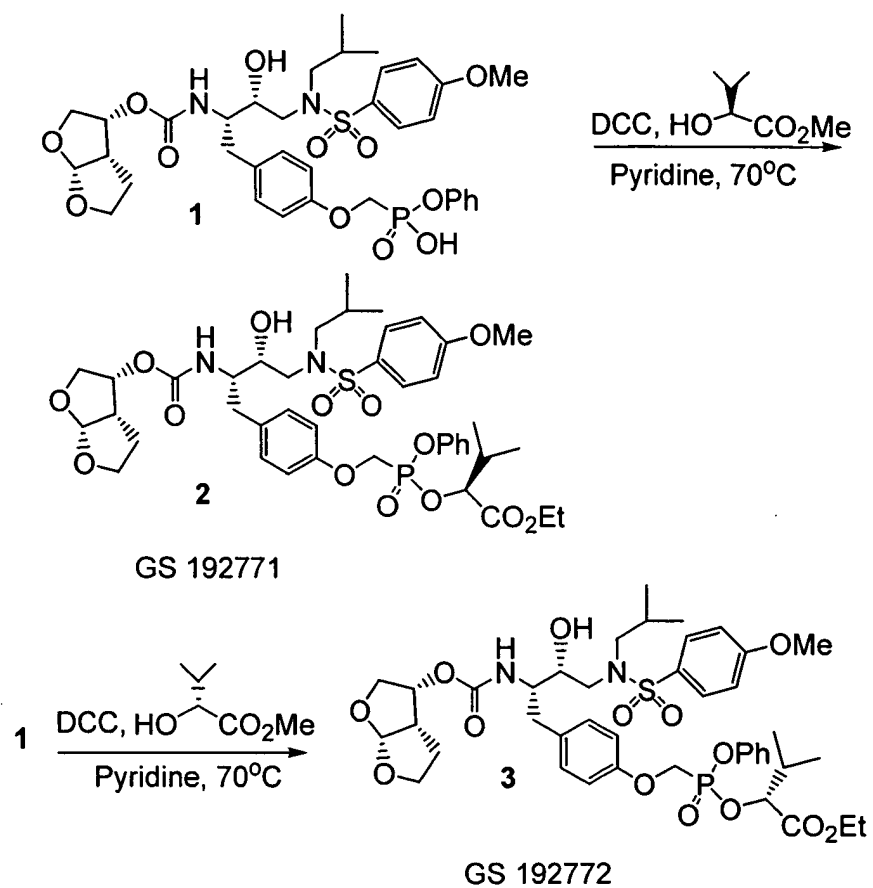
= 8.4 Hz, 2 H), 7.38 (br s, 2 H), 7.34-7.10 (m, 5 H), 6.98 (d,  $J$  = 8.8 Hz, 2 H), 5.72 (d,  $J$  = 5.0 Hz, 1 H), 5.50 (br s, 1 H), 5.19-5.01 (m, 2 H), 4.29-3.75 (m, 10 H), 3.85 (s, 3 H), 3.35-2.70 (m, 7 H), 2.23 (s, 3 H), 2.17-1.79 (m, 3 H), 1.54 (d,  $J$  = 6.9 Hz, 1.5 H), 1.48 (d,  $J$  = 6.8 Hz, 1.5 H), 1.25 (t,  $J$  = 7.2 Hz, 1.5 H), 1.16 (t,  $J$  = 7.2 Hz, 1.5 H), 0.92 (d,  $J$  = 6.6 Hz, 3 H), 0.87 (d,  $J$  = 6.6 Hz, 3 H).  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.0, 14.8.

#### Example V29

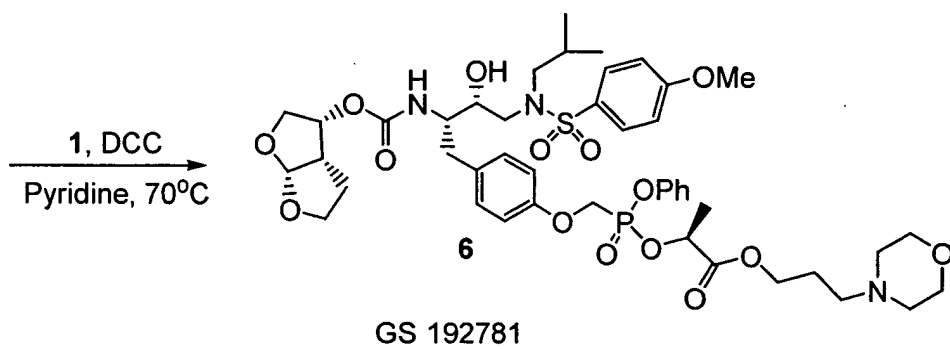
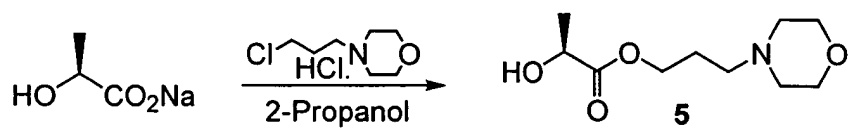
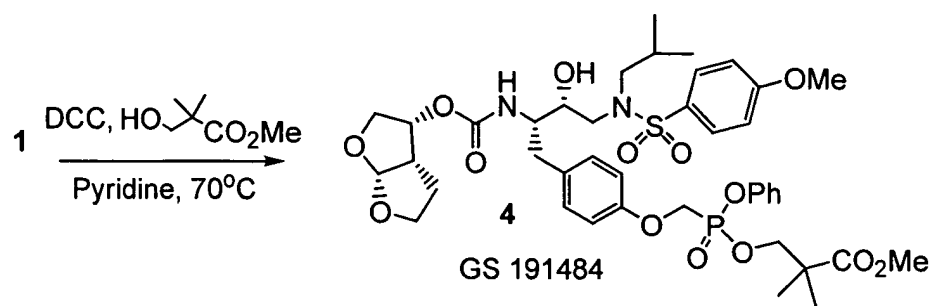
Compound 36: To a solution of compound **35** (44 mg, 0.045 mmol) in acetonitrile (1.0 mL) and DMSO (0.5 mL) was added phosphate buffered saline (pH 7.4, 5.0 mL) to give a cloudy white suspension. Porcine liver esterase (200  $\mu\text{L}$ ) was added and reaction mixture was stirred for 48 h at 38°C. Additional esterase (600  $\mu\text{L}$ ) was added and reaction was continued for 4 d. Reaction mixture was concentrated, diluted with MeOH and the resulting precipitate removed by filtration. Filtrate was concentrated and purified by reverse phase HPLC to give a white powder after lyophilization (7.2 mg, 21%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.95 (br s, 2 H), 7.76 (d,  $J$  = 8.4 Hz, 2 H), 7.64 (br s, 2 H), 7.13 (d,  $J$  = 8.7 Hz, 2 H), 5.68 (d,  $J$  = 5.1 Hz, 1 H), 5.14 (br s, 1 H), 4.77 (br s, 1 H), 4.35-3.59 (m, 8 H), 3.89 (s, 3 H), 3.45-2.62 (m, 10 H), 2.36-1.86 (m, 3 H), 1.44 (d,  $J$  = 6.3 Hz, 3 H), 0.92 (d,  $J$  = 6.6 Hz, 3 H), 0.84 (d,  $J$  = 6.6 Hz, 3 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  13.8.

## Example Section W

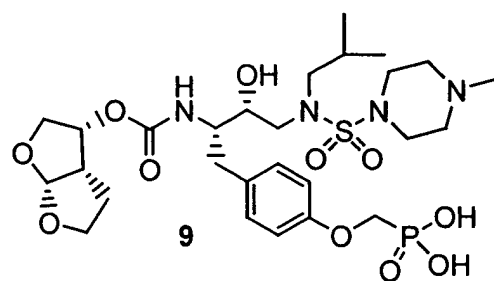
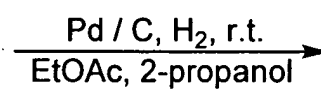
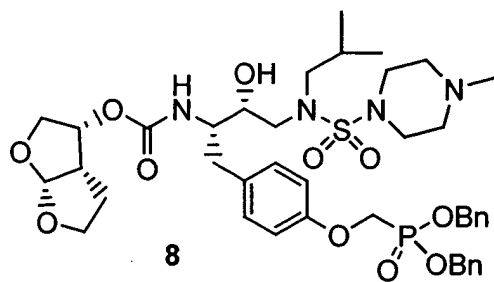
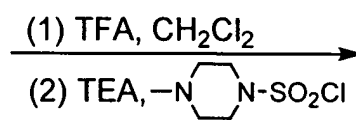
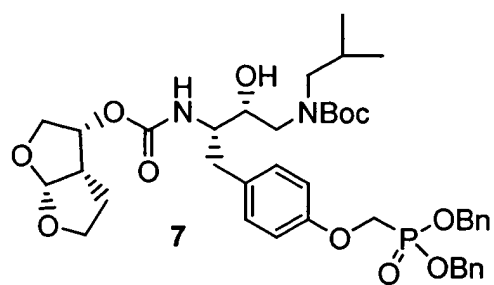
### Scheme W1



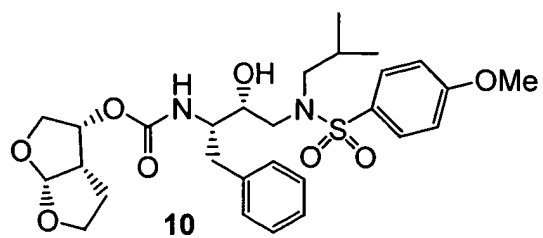
**Scheme W2**



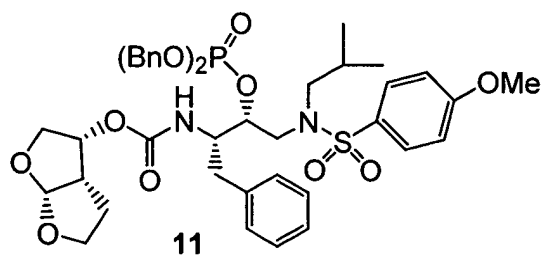
**Scheme W3**



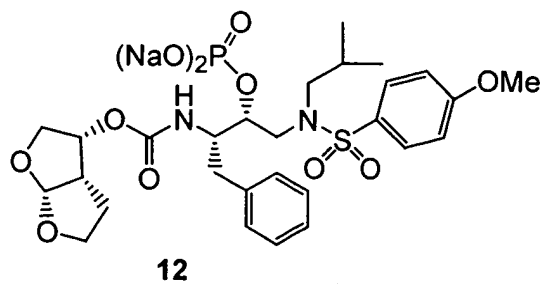
**Scheme W4**



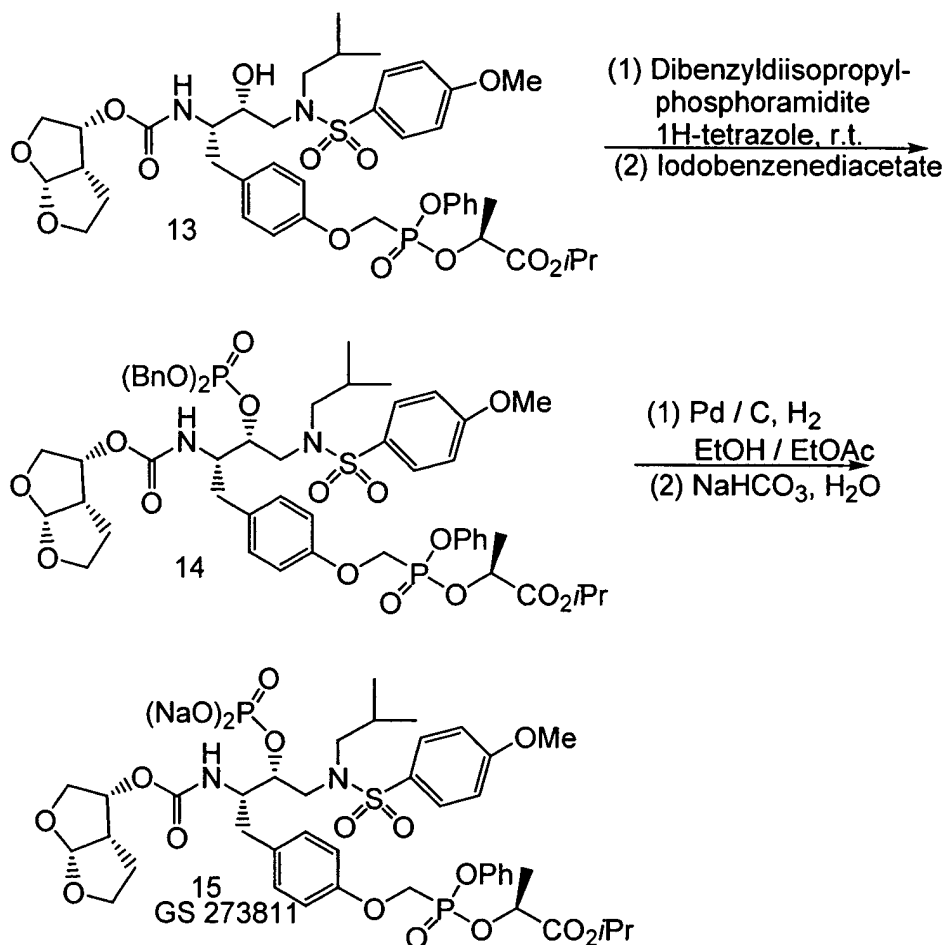
(1) Dibenzyl-diisopropyl-phosphoramidite  
1H-tetrazole, r.t.  
→  
(2) Iodobenzenediacetate



(1) Pd / C, H<sub>2</sub>  
EtOH / EtOAc  
→  
(2) NaHCO<sub>3</sub>, H<sub>2</sub>O



## Scheme W5



## Example W1

Monophospholactate 2: A solution of 1 (0.11 g, 0.15 mmol) and  $\alpha$ -hydroxyisovaleric acid ethyl-(S)-ester (71 mg, 0.49 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (35 mg, 28%, GS 192771, 1/1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.71 (d, J = 8.7 Hz, 2H), 7.36-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.94-6.84 (dd, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.00-4.85 (m, 3H), 4.55 (dd, 1H), 4.41 (dd, 1H), 4.22-4.07 (m,

2H), 3.96-3.68 (m, 9H), 3.12-2.74 (m, 7H), 2.29 (m, 1H), 1.85-1.57 (m, 3H), 1.24 (m, 3H), 1.05 (d,  $J = 6.6$  Hz, 3H), 0.98 (d,  $J = 6.6$  Hz, 3H), 0.9 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.7, 15.1.

#### Example W2

Monophospholactate 3: A solution of 1 (0.11 g, 0.15 mmol) and  $\alpha$ -hydroxyisovaleric acid ethyl-(R)-ester (71 mg, 0.49 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl,  $\text{H}_2\text{O}$ , saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (35 mg, 28%, GS 192772, 1/1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J = 8.7$  Hz, 2H), 7.35-7.13 (m, 7H), 6.98 (d,  $J = 8.7$  Hz, 2H), 6.93-6.83 (dd, 2H), 5.64 (d,  $J = 5.4$  Hz, 1H), 5.04-4.85 (m, 3H), 4.54 (dd, 1H), 4.39 (dd, 1H), 4.21-4.06 (m, 2H), 3.97-3.67 (m, 9H), 3.12-2.75 (m, 7H), 2.27 (m, 1H), 1.83-1.57 (m, 3H), 1.26 (m, 3H), 1.05 (d,  $J = 6.6$  Hz, 3H), 0.98 (d,  $J = 6.6$  Hz, 3H), 0.9 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.7, 15.1.

#### Example W3

Monophospholactate 4: A solution of 1 (0.10 g, 0.13 mmol) and methyl-2,2-dimethyl-3-hydroxypropionate (56  $\mu\text{L}$ , 0.44 mmol) in pyridine (1 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (91 mg, 0.44 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl,  $\text{H}_2\text{O}$ , saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (72 mg, 62%, GS 191484) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J = 8.7$  Hz, 2H), 7.34 (m, 2H), 7.25-7.14 (m, 5H), 7.00 (d,  $J = 9.0$  Hz, 2H), 6.87 (d,  $J = 8.7$  Hz, 2H), 5.65 (d,  $J = 5.4$  Hz, 1H), 5.05 (m, 2H), 4.38 (d,  $J = 9.6$  Hz, 2H), 4.32-4.20 (m, 2H), 4.00 (m, 2H), 3.87-3.63 (m, 12H), 3.12-2.78 (m, 7H), 1.85-1.67 (m, 3H), 1.20 (m, 6H), 0.91 (d,  $J = 6.6$  Hz, 3H), 0.88 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.0.

#### Example W4

Lactate 5: To a suspension of lactic acid sodium salt (5 g, 44.6 mmol) in 2-propanol (60 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (8.30 g, 44.6 mmol). The reaction mixture was heated to reflux for 18 h and cooled to room temperature. The solid was filtered and the filtrate was recrystallized from EtOAc / hexane to give the lactate (1.2 g, 12%).

#### Example W5

Monophospholactate 6: A solution of 1 (0.10 g, 0.13 mmol) and lactate 5 (0.10 g, 0.48 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and H<sub>2</sub>O. The EtOAc layer was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (30 mg, 24%, GS 192781, 1/1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, J = 8.7 Hz, 2H), 7.38-7.15 (m, 7H), 7.00 (d, J = 8.7 Hz, 2H), 6.91 (m, 2H), 5.65 (d, J = 3.3 Hz, 1H), 5.18-4.98 (m, 3H), 4.54 (dd, 1H), 4.42 (dd, 1H), 4.2 (m, 2H), 4.00-3.67 (m, 16H), 3.13-2.77 (m, 7H), 2.4 (m, 5H), 1.85-1.5 (m, 5H), 1.25 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.4, 15.4.

#### Example W6

Sulfonamide 8: A solution of dibenzylphosphonate 7 (0.1 g, 0.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and cooled to 0°C. Triethylamine (72 μL, 0.52 mmol) was added followed by the treatment of 4-methylpiperazinylsulfonyl chloride (25 mg, 0.13 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography

on silica gel (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the sulfonamide 8 (32 mg, 30%, GS 273835) as a white solid: <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 7.35 (m, 10H), 7.11 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.91 (m, 4H), 4.2 (d, J = 10.2 Hz, 2H), 4.0-3.69 (m, 6H), 3.4-3.19 (m, 5H), 3.07-2.75 (m, 5H), 2.45 (m, 4H), 2.3 (s, 3H), 1.89-1.44 (m, 7H), 0.93 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.3.

#### Example W7

Phosphonic Acid 9: To a solution of 8 (20 mg, 0.02 mmol) in EtOAc (2 mL) and 2-propanol (0.2 mL) was added 10% Pd/C (5 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (10 mg, 64%) as a white solid.

#### Example W8

Dibenzylphosphonate 11: A solution of 10 (85 mg, 0.15 mmol) and 1*H*-tetrazole (14 mg, 0.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was treated with Dibenzyl-diisopropylphosphoramidite (60 μL, 0.20 mmol) and stirred at room temperature overnight. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified by column chromatography to give the intermediate dibenzylphosphite (85 mg, 0.11 mmol) which was dissolved in CH<sub>3</sub>CN (2 mL) and treated with iodobenzenediacetate (51 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residue was partitioned between EtOAc and NaHCO<sub>3</sub>. The organic layer was washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the dibenzylphosphonate (45 mg, 52%) as a white solid.

#### Example W9

Disodium Salt of Phosphonic Acid 12: To a solution of 11 (25 mg, 0.03 mmol) in EtOAc (2 mL) was added 10% Pd/C (10 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid which was dissolved in H<sub>2</sub>O (1 mL) and treated with NaHCO<sub>3</sub> (2.53 mg, 0.06 mmol). The reaction mixture

was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (19.77 mg, 95%, GS 273777) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.81 (d,  $J$  = 9.0 Hz, 2H), 7.35 (d,  $J$  = 8.1 Hz, 2H), 7.27-7.09 (m, 5H), 5.57 (d,  $J$  = 5.1 Hz, 1H), 5.07 (m, 1H), 4.87-4.40 (m, 3H), 3.93-3.62 (m, 6H), 3.45-2.6 (m, 6H), 2.0 (m, 2H), 1.55 (m, 1H), 0.95-0.84 (m, 6H).

#### Example W10

Dibenzylphosphonate 14: A solution of 13 (0.80 g, 0.93 mmol) and 1*H*-tetrazole (98 mg, 1.39 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL) was treated with dibenzyl-diisopropylphosphoramidite (0.43 mL, 1.39 mmol) and stirred at room temperature overnight. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude product was purified by column chromatography to give the intermediate dibenzylphosphite (0.68 g, 67%). To a solution of the dibenzylphosphite (0.39 g, 0.35 mmol) in  $\text{CH}_3\text{CN}$  (5 mL) was added iodobenzenediacetate (0.17 g, 0.53 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated. The residue was partitioned between EtOAc and  $\text{NaHCO}_3$ . The organic layer was washed with  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the dibenzylphosphonate (0.35 g, 88%) as a white solid.

#### Example W11

Disodium Salt of Phosphonic Acid 15: To a solution of 14 (0.39 g, 0.35 mmol) in EtOAc (30 mL) was added 10% Pd/C (0.10 g). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid, which was dissolved in  $\text{H}_2\text{O}$  (3 mL) and treated with  $\text{NaHCO}_3$  (58 mg, 0.70 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (0.31 g, 90%, GS 273811) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.81 (d,  $J$  = 9.0 Hz, 2H), 7.43-7.2 (m, 7H), 7.13 (d,  $J$  = 9.0 Hz, 2H), 6.9 (m, 2H), 5.55 (d,  $J$  = 4.8 Hz, 1H), 5.07 (m, 2H), 4.87 (m, 1H), 4.64-4.4 (m, 4H), 3.93-3.62 (m, 9H), 3.33-2.63 (m, 5H), 2.11 (m, 1H), 1.6-1.42 (m, 4H), 1.38-1.25 (m, 7H), 0.95 (d,  $J$  = 6.3 Hz, 3H), 0.84 (d,  $J$  = 6.3 Hz, 3H).

## **Saquinavir-like phosphonate protease inhibitors (SLPPI)**

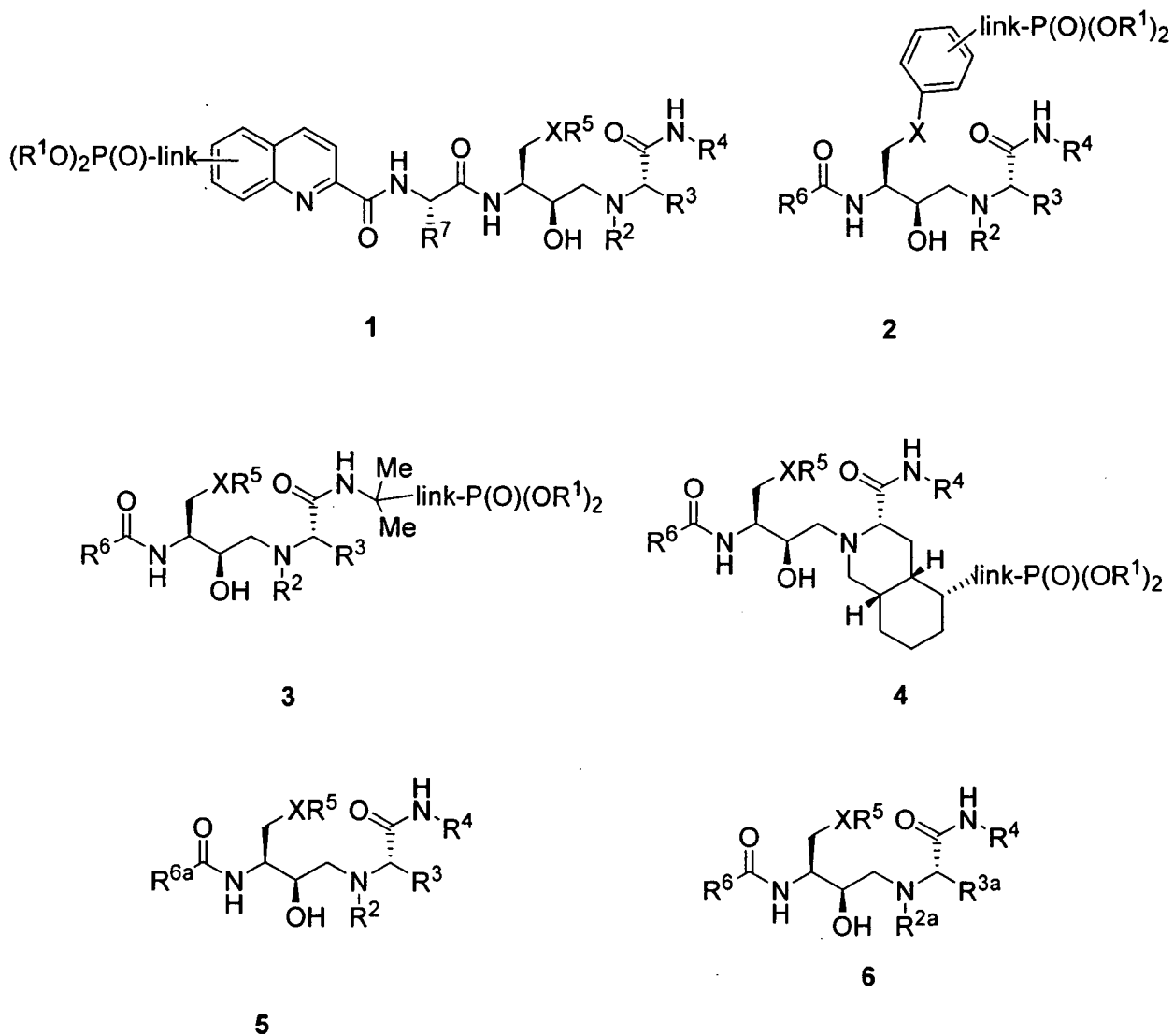
### **Preparation of the intermediate phosphonate esters**

The structures of the intermediate phosphonate esters **1** to **6**, and the structures for the component groups  $R^1$ ,  $R^4$  and  $R^7$  of this invention are shown in Chart 1.

The structures of the  $R^2NHCH(R^3)CONHR^4$  and  $R^5XCH_2$  components are shown in Charts **2** and **2a**, and the structures of the  $R^6COOH$  components are shown in Charts **3a**, **3b** and **3c**. Specific stereoisomers of some of the structures are shown in Charts **1**, **2** and **3**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **6**. Subsequent chemical modifications to the compounds **1** to **6**, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds **1** to **6** incorporate a phosphonate moiety  $(R^1O)_2P(O)$  connected to the nucleus by means of a variable linking group, designated as “link” in the attached structures. Charts **4** and **5** illustrate examples of the linking groups present in the structures **1** – **5**, and in which “etc” refers to the scaffold, *e.g.*, saquinavir.

Chart 1



$R^{6a}$  = phosphonate-containing  $R^6$

$R^{2a}$ ,  $R^{3a}$  = phosphonate-containing  $R^2$  or  $R^3$

$R^1$  = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

$R^4$  =  $\text{CH}(\text{CH}_3)_3$ ;  $\text{CH}_2\text{CF}_3$ ;  $\text{CH}_2\text{C}_6\text{H}_4(\text{CH}_3)_2$

$R^7$  = alkyl,  $\text{CH}_2\text{SO}_2\text{CH}_3$ ,  $\text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3$ ,  $\text{CH}_2\text{CONH}_2$ ,  $\text{CH}_2\text{SCH}_3$ , imidaz-4-ylmethyl,  $\text{CH}_2\text{NHAc}$ ,  $\text{CH}_2\text{NHCOCF}_3$

X = S, direct bond

Chart 2

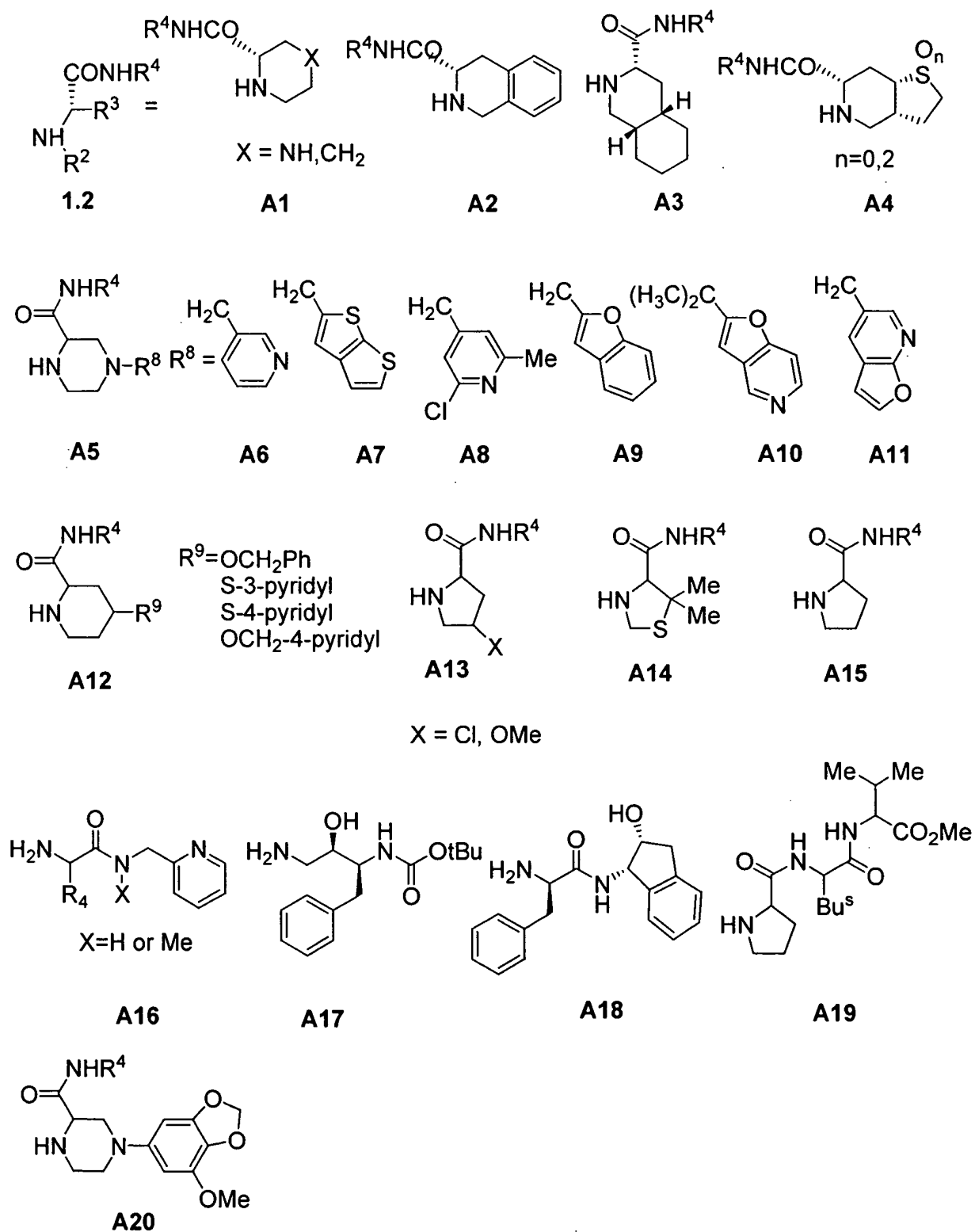
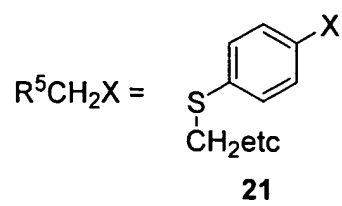
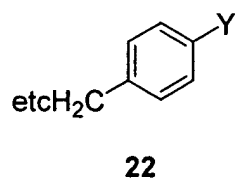


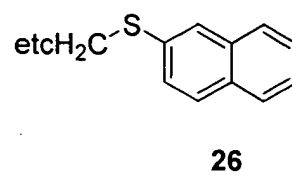
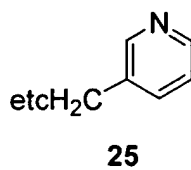
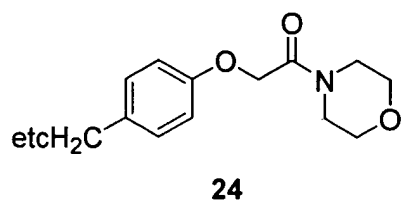
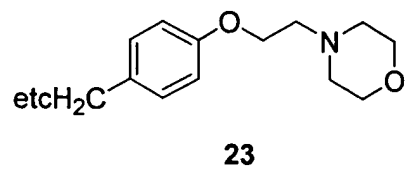
Chart 2a



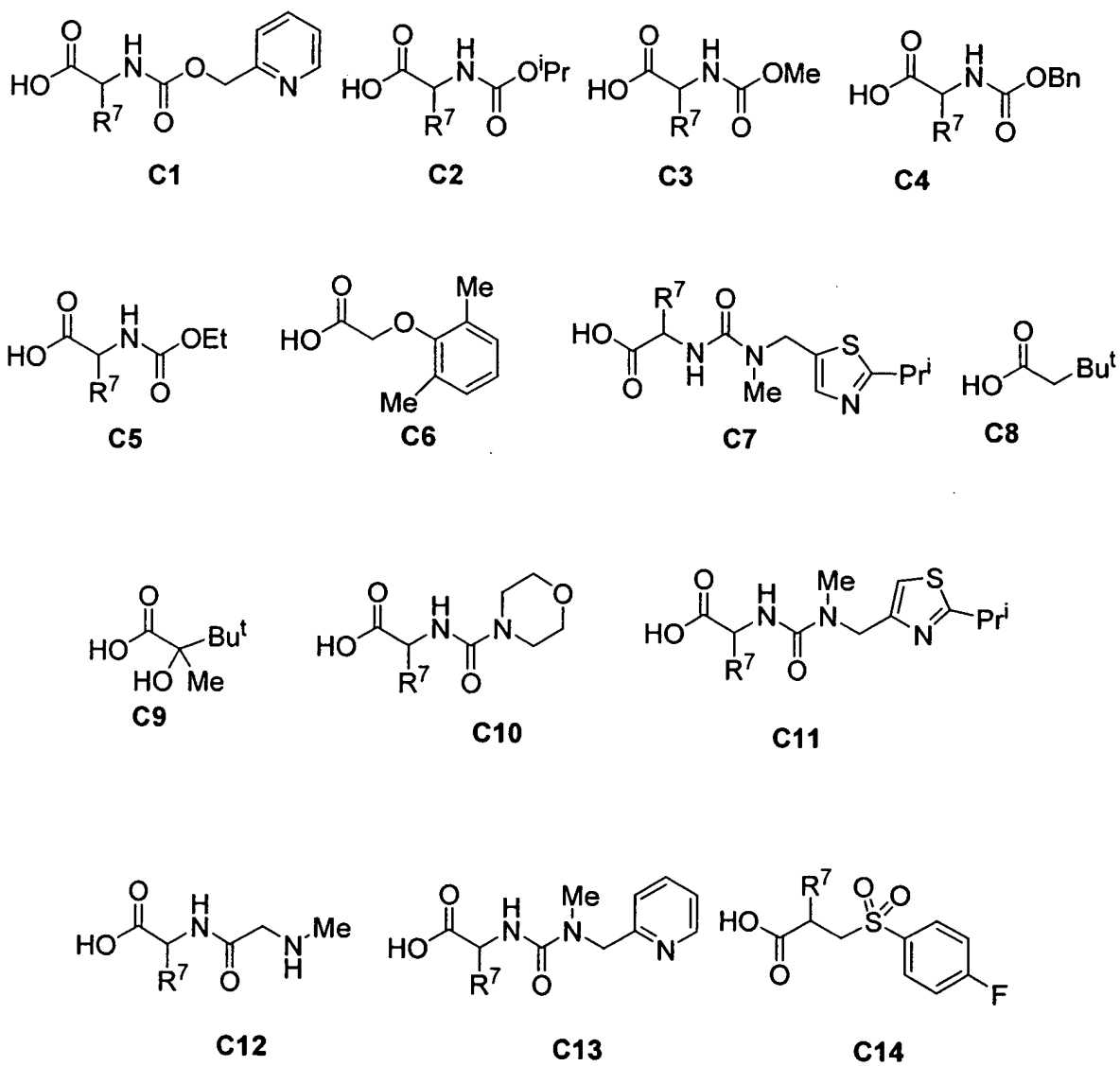
X = H, F

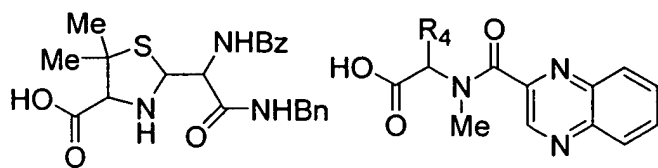


Y = H, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>



**Chart 3a Structures of the R<sup>6</sup>COOH components**

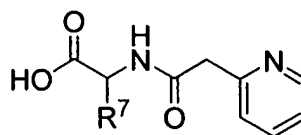




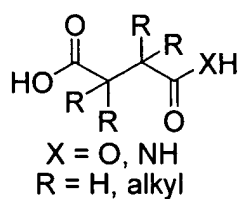
**C15**



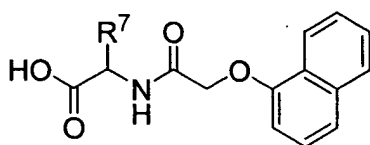
**C16**



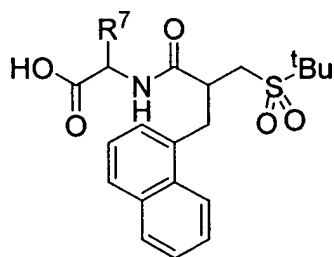
**C17**



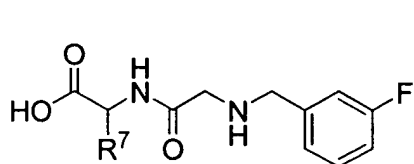
**C18**



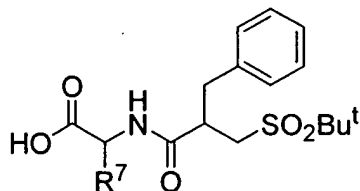
**C19**



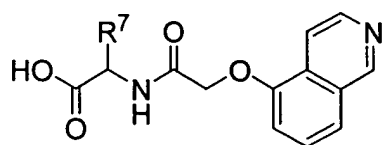
**C20**



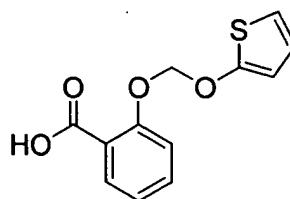
**C21**



**C22**



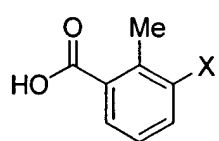
**C23**



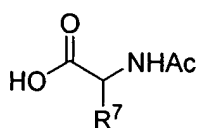
**C24**

R<sup>7</sup> = alkyl, CH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CONH<sub>2</sub>, CH<sub>2</sub>SCH<sub>3</sub>, imidaz-4-ylmethyl, CH<sub>2</sub>NHAc, CH<sub>2</sub>NHCOCF<sub>3</sub>

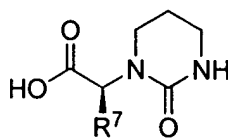
**Chart 3b Structures of the R<sup>6</sup>COOH components**



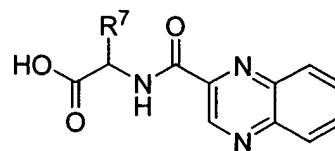
**C25**  
X = OH, NH<sub>2</sub>



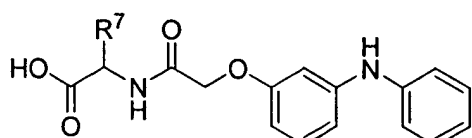
**C26**



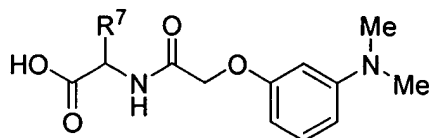
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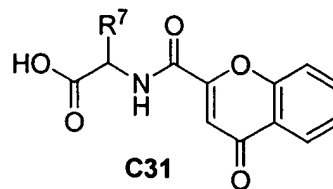
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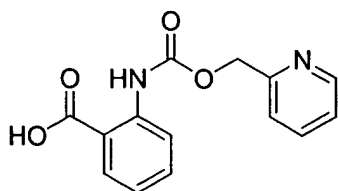
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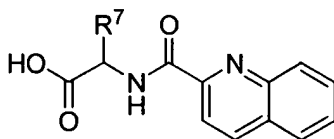
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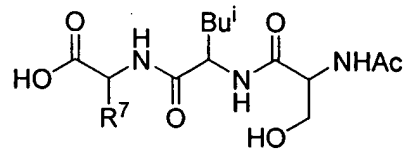
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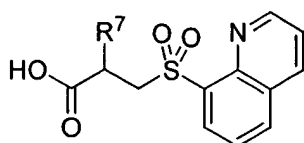
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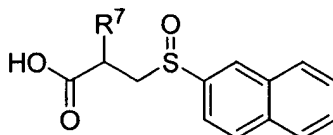
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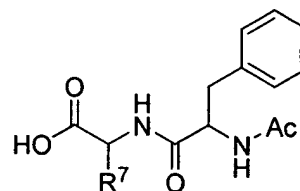
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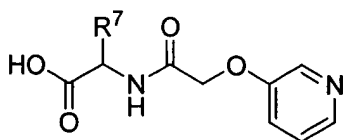
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**C36**



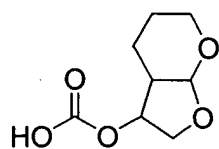
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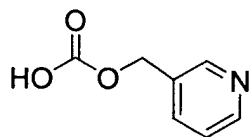
**C38**

R<sup>7</sup> = alkyl, CH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CONH<sub>2</sub>, CH<sub>2</sub>SCH<sub>3</sub>, imidaz-4-ylmethyl, CH<sub>2</sub>NHAc, CH<sub>2</sub>NHCOCF<sub>3</sub>

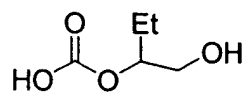
**Chart 3c Structures of the R<sup>6</sup>COOH components**



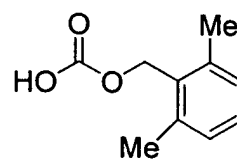
**C38**



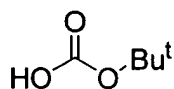
**C39**



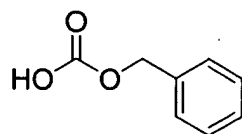
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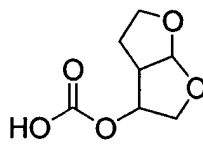
**C41**



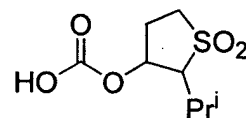
**C42**



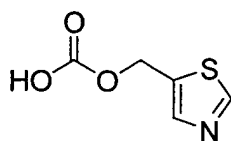
**C43**



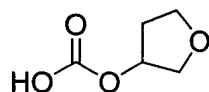
**C44**



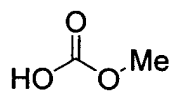
**C45**



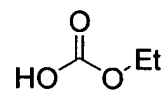
**C46**



**C47**

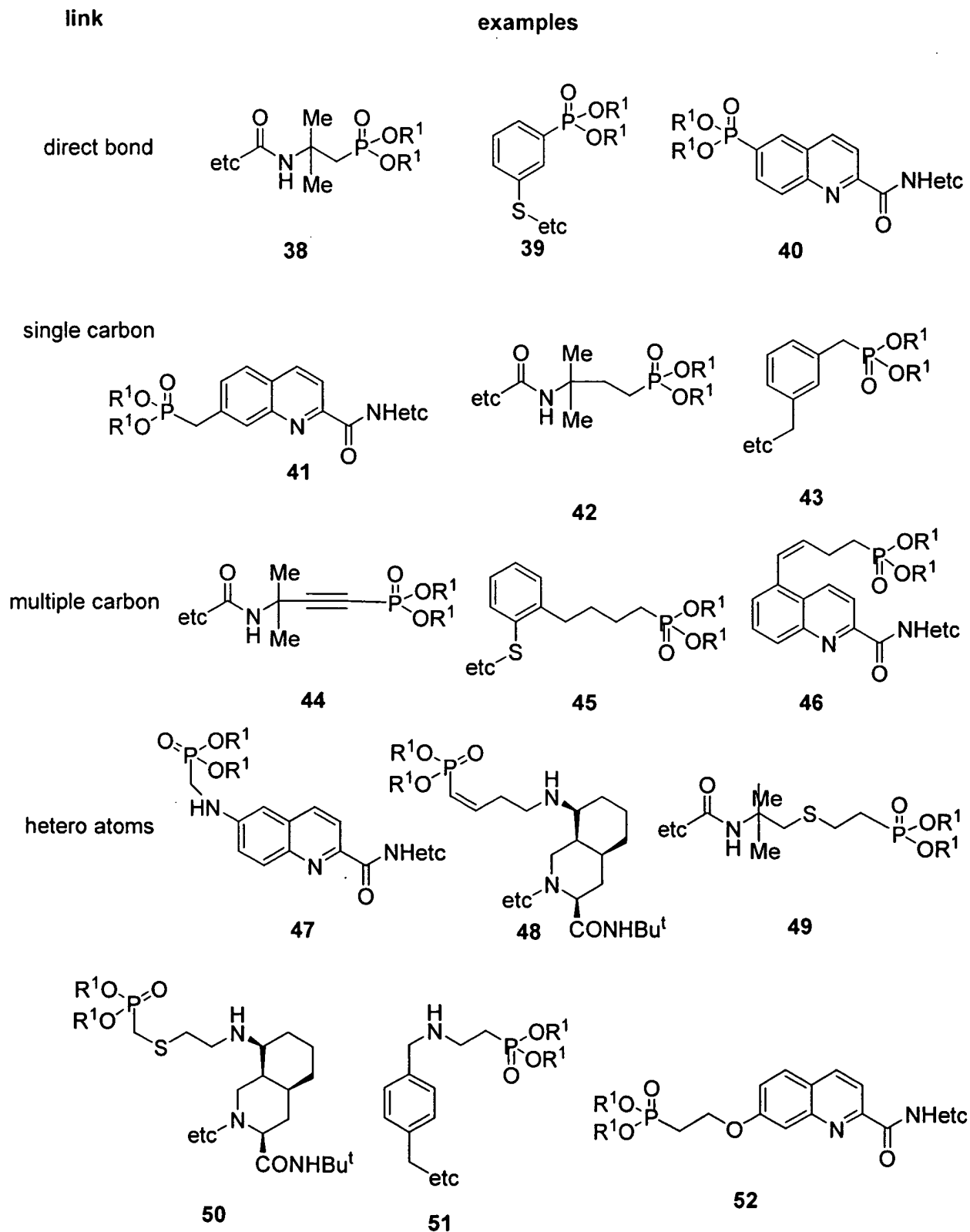


**C48**

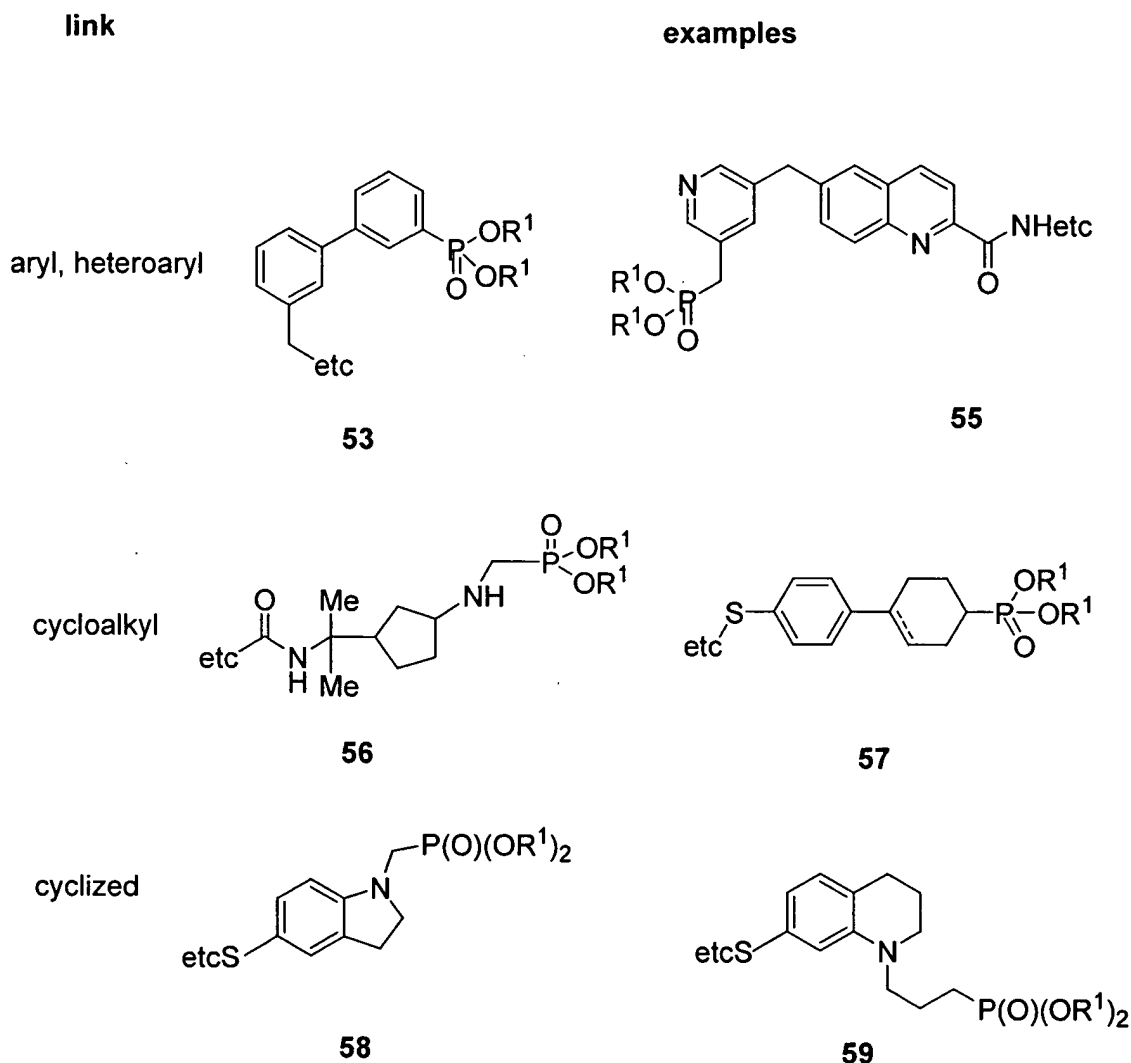


**C49**

**Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety**



**Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.**



Schemes 1 - 69 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1- 4, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 5 and 6, in which the phosphonate moiety is incorporated into the groups  $R^6\text{COOH}$  and  $R^2\text{NHCH}(R^3)\text{CONHR}^4$ , are also described below.

#### Protection of reactive substituents

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art.

Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

### **Preparation of the phosphonate intermediates 1**

Scheme 1 illustrates one method for the preparation of the phosphonate esters **1.6** in which X is a direct bond. In this procedure, an amine  $R^2NHCH(R^3)CONHR^4$  **1.2** is reacted with an epoxide **1.1** to afford the aminoalcohol **1.3**. The preparation of the epoxide **1.1** is described below, (Scheme 2) The preparation of aminoalcohols by reaction between an amine and an epoxide is described, for example, in Advanced Organic Chemistry, by J. March, McGraw Hill, 1968, p 334. In a typical procedure, equimolar amounts of the reactants are combined in a polar solvent such as an alcohol or dimethylformamide and the like, at from ambient to about 100°, for from 1 to 24 hours, to afford the product **1.3**. The carbobenzyloxy protecting group is then removed. The removal of carbobenzyloxy protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 335. The reaction can be effected by means of catalytic hydrogenation in the presence of hydrogen or a hydrogen donor, by reaction with a Lewis acid such as aluminum chloride or boron tribromide, or by basic hydrolysis, for example employing barium hydroxide in an aqueous organic solvent mixture. Preferably, the protected amine **1.3** is converted into the free amine **1.4** by means of hydrogenation over 10% palladium on carbon catalyst in ethanol, as described in US Patent 5196438. The amine product **1.4** is then reacted with a carboxylic acid **1.5** to afford the amide **1.6**. The coupling reaction of amines **1.4** and a carboxylic acid **1.5** can be effected under a variety of conditions, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid can be activated by conversion to an imidazolide, mixed anhydride or active ester such as, for example, the ester with hydroxybenztriazole or N-hydroxysuccinimide. Alternatively, the reactants can be combined in the presence of a carbodiimide, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, to afford the amide product **1.6**. Preferably, equimolar amounts of the amine and the carboxylic acid are reacted in tetrahydrofuran at ca. -10°, in the presence of dicyclohexylcarbodiimide, as described in U.S. Patent 5,196,438, to afford the amide **1.6**. The carboxylic acid **1.5** employed in the above reaction is obtained by means of the reaction between

the substituted quinoline-2-carboxylic acid **1.7**, in which the substituent A is either the group  $\text{link-P(O)(OR}^1\text{)}_2$  or a precursor group thereto, such as [OH], [SH], Br, as described below, and an aminoacid **1.8**. The reaction is performed under similar conditions to those described above for the preparation of the amide **1.6**. Preferably, the quinoline carboxylic acid **1.7** is reacted with N-hydroxy succinimide and a carbodiimide to afford the hydroxysuccinimide ester, which is then reacted with the aminoacid **1.8** in dimethylformamide at ambient temperature for 2-4 days, as described in U.S. Patent 5,196,438, to afford the amide product **1.5**. The preparation of the substituted quinoline carboxylic acids **1.7** is described below, Schemes 24-27.

Scheme 2 illustrates the preparation of the epoxides **1.1** used above in Scheme 1. The preparation of the epoxide **1.1** in which R10 is H is described in *J. Med. Chem.*, 1997, 40, 3979. Analogs in which R10 is one of the substituents defined in Chart 2 are prepared as shown in Scheme 2. A substituted phenylalanine **2.1** is first converted into the benzyloxycarbonyl derivative **2.2**. The preparation of benzyloxycarbonyl amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The aminoacid **2.1** is reacted with benzyl chloroformate or dibenzyl carbonate in the presence of a suitable base such as sodium carbonate or triethylamine, to afford the protected amine product **2.2**. The conversion of the carboxylic acid **2.2** into the epoxide **1.1** for example using the sequence of reactions which is described in *J. Med. Chem.*, 1994, 37, 1758, is then effected. The carboxylic acid is first converted into an activated derivative such as the acid chloride **2.3**, in which X is Cl, for example by treatment with oxalyl chloride, or into a mixed carbonate, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **2.4**. The reaction is performed by the addition of a solution of the activated carboxylic acid derivative to an ethereal solution of three or more molar equivalents of diazomethane at 0°C. The diazoketone is converted into the chloroketone **2.5** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether, as described in *J. Med. Chem.*, 1997, 40, 3979. The latter compound is then reduced, for example by the use of an equimolar amount of sodium borohydride in an ethereal solvent such as tetrahydrofuran at 0°C, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **2.6** is separated by chromatography. The chlorohydrin **2.6** is then converted into the epoxide **1.1** by treatment with a base such as an alkali metal hydroxide in an alcoholic solvent, for example as described in *J. Med. Chem.*, 1997, 40, 3979. Preferably, the

compound **2.6** is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **1.1**.

Scheme 3 illustrates the preparation of the amine reactant  $R^2NHCH(R^3)CONHR^4$  (**1.2**) employed above (Scheme 1). In this procedure, the carboxylic acid  $R^2NHCH(R^3)COOH$  **3.1** is first converted into the N-protected analog **3.2**, for example by reaction with benzyloxychloroformate and triethylamine in tetrahydrofuran. The carboxyl group is then activated, for example by conversion to the acid chloride or a mixed anhydride, or by reaction with isobutyl chloroformate, as described in *Chimia*, 50, 532, 1996 and in *Synthesis*, 1972, 453, and the activated derivative is then reacted with the amine  $R^4NH_2$  to produce the amide **3.4**. Deprotection, for example as described above, then affords the free amine **1.2**.

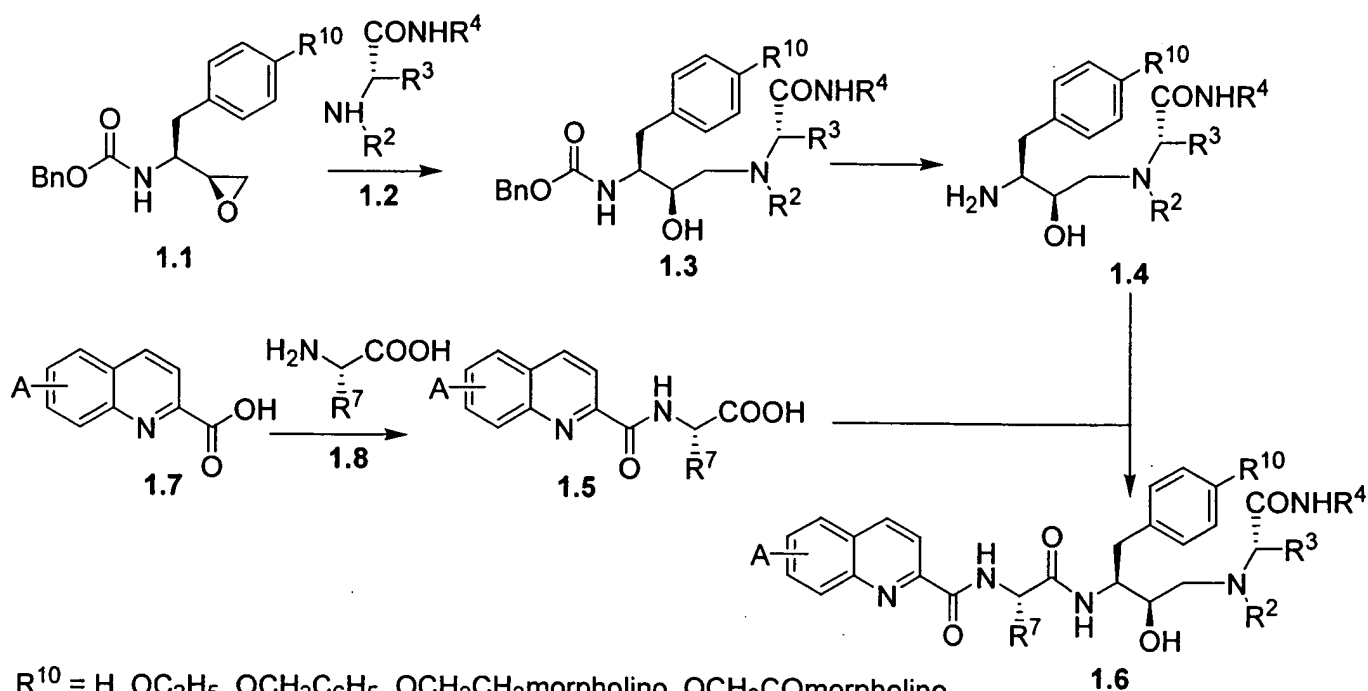
Scheme 4 depicts an alternative method for the preparation of the compounds **1** in which X is a direct bond. In this procedure, a hydroxymethyl-substituted oxazolidinone **4.1** is converted into an activated derivative **4.2** which is then reacted with the amine  $R^2NHCH(R^3)CONHR^4$  (**1.2**) to afford the amide **4.3**. The preparation of the hydroxymethyl-substituted oxazolidinone **4.1** is described below, (Scheme 5) The hydroxyl group can be converted into a bromo derivative, for example by reaction with triphenylphosphine and carbon tetrabromide, as described in *J. Am. Chem. Soc.*, 92, 2139, 1970, or a methanesulfonyloxy derivative, by reaction with methanesulfonyl chloride and a base, or, preferably, into the 4-nitrobenzenesulfonyloxy derivative **4.2**, by reaction in a solvent such as ethyl acetate or tetrahydrofuran, with 4-nitrobenzenesulfonyl chloride and a base such as triethylamine or N-methylmorpholine, as described in WO 9607642. The nosylate product **4.2** is then reacted with the amine component **1.2** to afford the displacement product **4.3**. Equimolar amounts of the reactants are combined in an inert solvent such as dimethylformamide, acetonitrile or acetone, optionally in the presence of an organic or inorganic base such as triethylamine or sodium carbonate, at from about 0°C to 100°C to afford the amine product **4.3**. Preferably, the reaction is performed in methyl isobutyl ketone at 80°C, in the presence of sodium carbonate, as described in WO 9607642. The oxazolidinone group present in the product **4.3** is then hydrolyzed to afford the hydroxyamine **4.4**. The hydrolysis reaction is effected in the presence of aqueous solution of a base such as an alkali metal hydroxide, optionally in the presence of an organic co-solvent. Preferably, the oxazolidinone compound **4.3** is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine **4.4**. This product is then

reacted with the carboxylic acid or activated derivative thereof, **1.5**, the preparation of which is described above, to afford the product **1.6**. The amide-forming reaction is conducted under the same conditions as described above, (Scheme 1)

Scheme 5 depicts the preparation of the hydroxymethyl oxazolidinones **4.1**, which are utilized in the preparation of the phosphonate esters **1**, as described above in Scheme 4. In this procedure, phenylalanine, or a substituted derivative thereof, **2.1**, in which R<sup>10</sup> is as defined in Chart 2, is converted into the phthalimido derivative **5.1**. The conversion of amines into phthalimido derivatives is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine **5.1**. Preferably, the aminoacid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride **5.2**, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride **5.2**, X = Cl, is then converted into the aldehyde **5.3** by means of a reduction reaction. This procedure is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride or triethylsilane. Preferably, the acid chloride **5.2** X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of butylene oxide, as described in WO 9607642, to afford the aldehyde **5.3**. The aldehyde **5.3** is then transformed into the cyanohydrin derivative **5.4**. The conversion of aldehydes into cyanohydrins is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 211. For example, the aldehyde **5.3** is converted into the cyanohydrin **5.4** by reaction with trimethylsilyl cyanide in an inert solvent

such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described in WO 9607642, or by alternative methods described therein. The cyanohydrin is then subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the aminoacid **5.5**. The hydrolysis reactions are effected by the use of aqueous mineral acid. For example, the substrate **5.4** is reacted with aqueous hydrochloric acid at reflux, as described in WO 9607642, to afford the carboxylic acid product **5.5**. The aminoacid is then converted into a carbamate, for example the ethyl carbamate **5.6**. The conversion of amines into carbamates is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate, for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to afford the carbamate **5.6**. For example, the aminoacid **5.5** is reacted, in aqueous solution, with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as described in WO 9607642, to afford the carbamate **5.6**. The latter compound is then transformed into the oxazolidinone **5.7**, for example by treatment with aqueous sodium hydroxide at ambient temperature, as described in WO 9607642. The resultant carboxylic acid is transformed into the methyl ester **5.8** by means of a conventional esterification reaction. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for example an alkyl bromide. For example, the carboxylic acid **5.7** is converted into the methyl ester **5.8** by treatment with methanol at reflux temperature, in the presence of a catalytic amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the compound **5.8** is then reduced to yield the corresponding carbinol **4.1**. The reduction of carboxylic esters to the carbinols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing agents such as borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride and the like. For example, the ester **5.8** is reduced to the carbinol **4.1** by reaction with sodium borohydride in ethanol at ambient temperature, as described in WO 9607642.

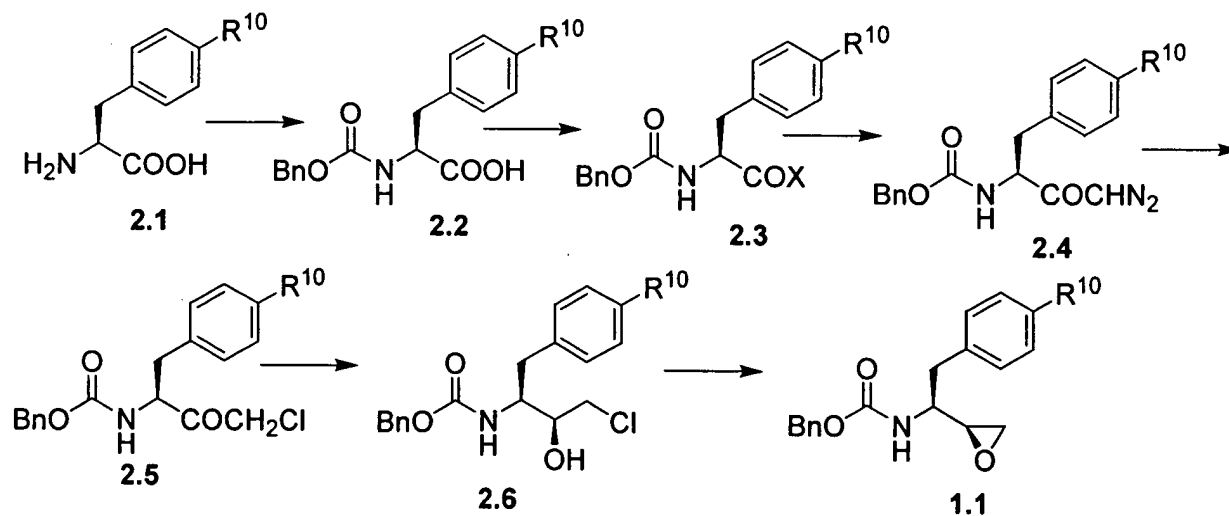
**Scheme 1**



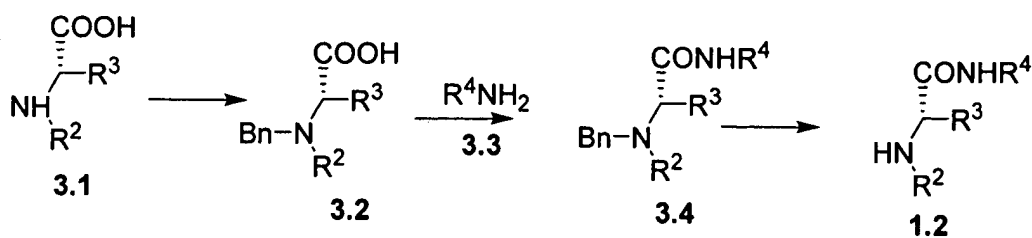
$R^{10} = \text{H}, \text{OC}_2\text{H}_5, \text{OCH}_2\text{C}_6\text{H}_5, \text{OCH}_2\text{CH}_2\text{morpholino}, \text{OCH}_2\text{COMorpholino}$

$A = [\text{OH}], [\text{SH}], [\text{NH}_2], \text{Br}$  etc or link- $\text{P}(\text{O})(\text{OR}^1)_2$

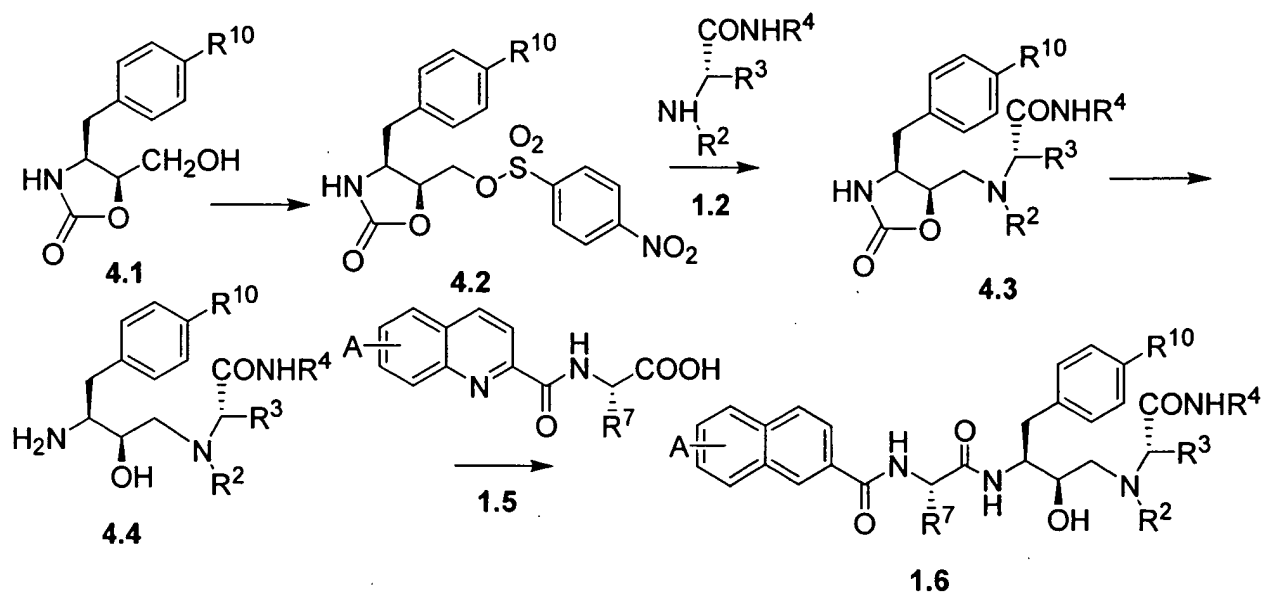
**Scheme 2**



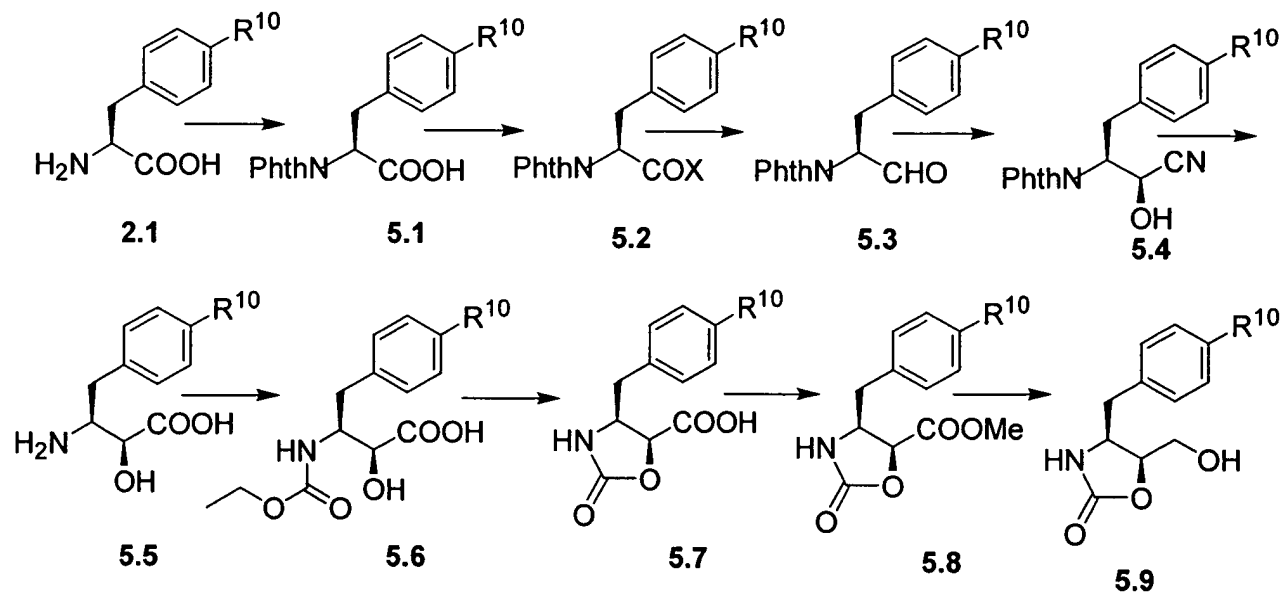
**Scheme 3**



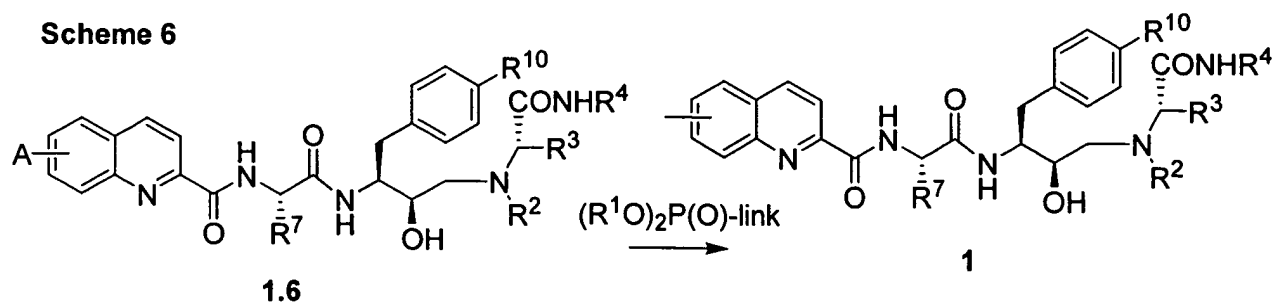
# Scheme 4



# Scheme 5

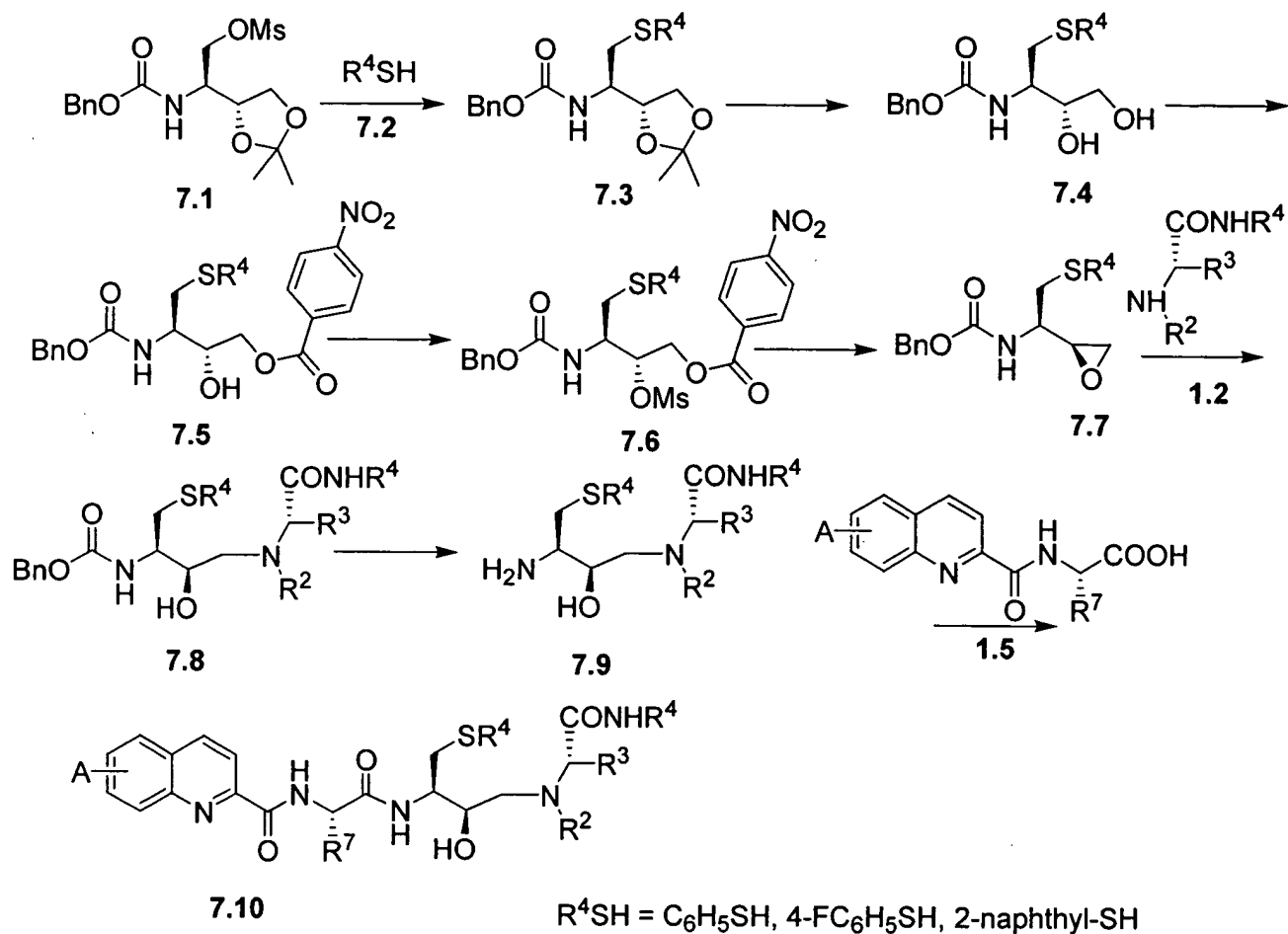


# Scheme 6

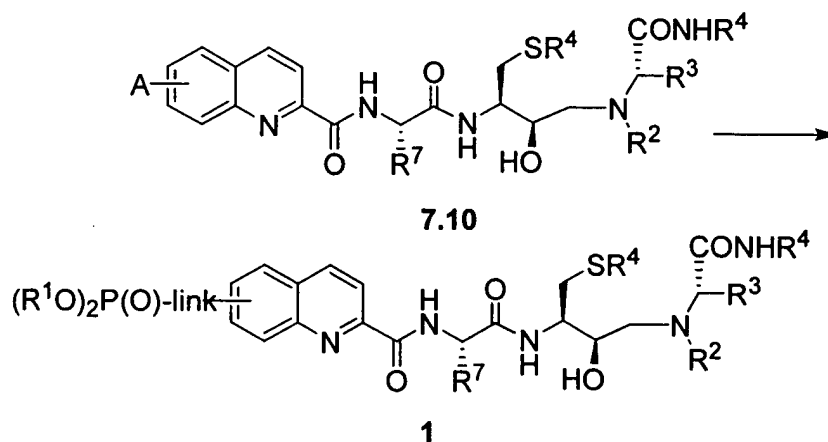


The procedures illustrated in Schemes 1 and 4 depict the preparation of the compounds **1.6** in which X is a direct bond, and in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 6 illustrates the conversion of compounds **1.6** in which A is a precursor to the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> into the compounds **1**. Procedures for the conversion of the substituent A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> are illustrated below, (Schemes 24 - 69). In the procedures illustrated above, Schemes 1, 4 and in the procedures illustrated below (Schemes 24-69) for the preparation of the phosphonate esters **2-6**, compounds in which the group A is a precursor to the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> may be converted into compounds in which A is link-P(O)(OR<sup>1</sup>)<sub>2</sub> at any appropriate stage in the reaction sequence, or, as shown in Scheme 6, at the end of the sequence. The selection of an appropriate stage to effect the conversion of the group A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> is made after consideration of the nature of the reactions involved in the conversion, and the stability of the various components of the substrate to those conditions.

# **Scheme 7**



# **Scheme 8**



Scheme 7 illustrates the preparation of the compounds **1** in which the substituent X is S, and in which the group A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below.

In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **7.1**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R<sup>4</sup>SH **7.2**, as defined above, to afford the thioether **7.3**.

The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether **7.3**. Preferably the mesylate **7.1** is reacted with an equimolar amount of the thiol R<sup>4</sup>SH, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product **7.3**. The 1,3-dioxolane protecting group present in the compound **7.3** is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **7.4**. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p. 191. For example, the 1,3-dioxolane compound **7.3** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane **7.3** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product **7.4**.

The primary hydroxyl group of the diol **7.4** is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol **7.4** and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester **7.5**. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester **7.6**. Preferably, equimolar amounts of the carbinol **7.5** and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the

mesylate **7.6**. The compound **7.6** is then subjected to a hydrolysis-cyclization reaction to afford the oxirane **7.7**. The mesylate or analogous leaving group present in **7.6** is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane **7.7** with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester **7.6** is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate **7.6** is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane **7.7**.

The oxirane compound **7.7** is then subjected to regiospecific ring-opening reaction by treatment with a secondary amine **1.2**, to give the aminoalcohol **7.8**. The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the product **7.8**. Preferably, equimolar amounts of the reactants **7.7** and **1.2** are reacted in aqueous methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford the aminoalcohol **7.8**. The carbobenzyloxy (cbz) protecting group in the product **7.8** is removed to afford the free amine **7.9**. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic hydrolysis.

For example, the cbz-protected amine **7.8** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **7.9**. Preferably, the cbz group is removed by the reaction of **7.8** with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to afford the amine **7.9**. The amine **7.9** so obtained is next acylated with a carboxylic acid or activated derivative **1.5**, using the conditions described above for the conversion of the amine **1.4** into the amide **1.6** (Scheme 1), to yield the final amide product **7.10**.

The procedures illustrated in Scheme 7 depict the preparation of the compounds **1** in which X is S, and in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 8 illustrates the conversion of compounds **7.10** in which A is a precursor to the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> into the compounds **1**. Procedures for the conversion of the substituent A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> are illustrated below, (Schemes 24 - 69).

The reactions illustrated in Schemes 1-7 illustrate the preparation of the compounds **1** in which A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as, for example,

optionally protected OH, SH, NH, as described below. Scheme 8 depicts the conversion of the compounds 1 in which A is OH, SH, NH, as described below, into the compounds 1 in which A is the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>. Procedures for the conversion of the group A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> are described below, (Schemes 24-69).

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below, (Scheme 54)

### Preparation of the phosphonate intermediates 2

Scheme 9 depicts the one method for the preparation of the compounds 2 in which X is a direct bond, and in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below. In this procedure, the hydroxymethyl oxazolidinone 9.1, the preparation of which is described below, is converted into an activated derivative, for example the 4-nitrobenzenesulfonate 9.2. The conditions for this transformation are the same as those described above (Scheme 4) for the conversion of the carbinol 4.1 into the nosylate 4.2. The activated ester 9.2 is then reacted with the amine 1.2, under the same conditions as described above for the preparation of the amine 4.3 to afford the oxazolidinone amine 9.3. The oxazolidinone group is then hydrolyzed by treatment with aqueous alcoholic base, to produce the primary amine 4.4. For example, the oxazolidinone 9.3 is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine product 9.4. The latter compound is then coupled with the carboxylic acid 9.6, to afford the amide 9.5. The conditions for the coupling reaction are the same as those described above for the preparation of the amide 1.6.

The phosphonate esters 2 - 6 which incorporate the group R<sup>6</sup> CO derived formally from the carboxylic acids depicted in Chart 2c contain a carbamate group. Various methods for the preparation of carbamates are described below, (Scheme 55)

Scheme 10 illustrates an alternative method for the preparation of the compounds 2 in which X is a direct bond, and in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below. In this procedure, the oxirane 10.1, the preparation of which is described below, is reacted with the amine 1.2 to afford the aminoalcohol 10.2. The reaction is conducted under the same conditions as are described above

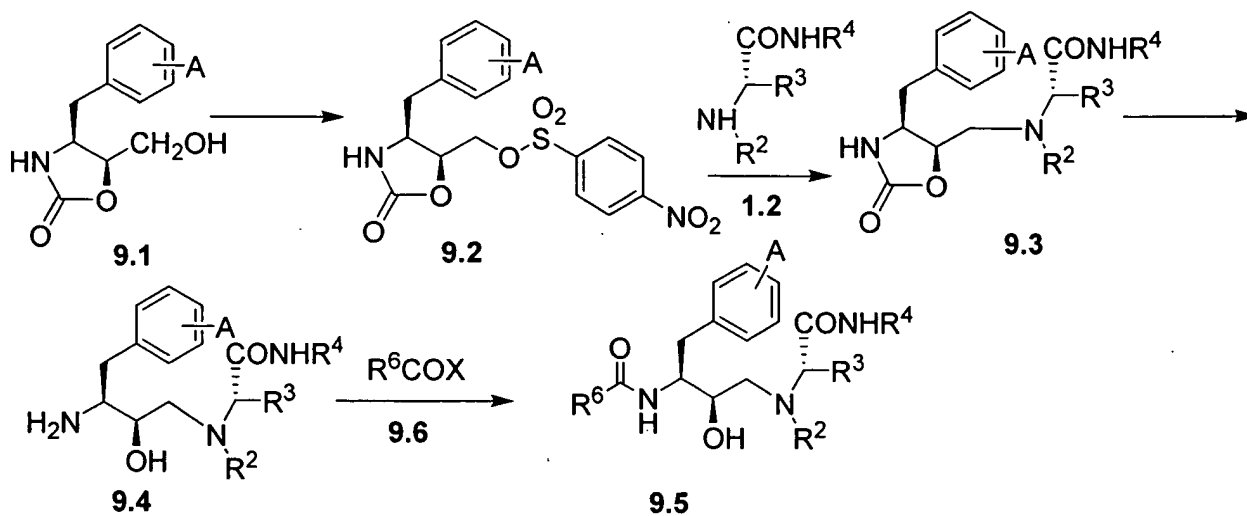
for the preparation of the aminoalcohol **1.3**. (Scheme 1) The benzyloxycarbonyl protecting group is then removed from the product **10.2** to afford the free amine **10.3**. The conditions for the debenzilation reaction are the same as those described above for the debenzilation of the compound **1.3**. The amine **10.3** is then coupled with the carboxylic acid **9.6** to produce the amide **9.5**, employing the same conditions as are described above (Scheme 9).

The procedures illustrated in Schemes 9 and 10 depict the preparation of the compounds **9.5** in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 11 illustrates the conversion of compounds **9.5** in which A is a precursor to the group  $\text{link-P(O)(OR}^1)_2$  into the compounds **2**. Procedures for the conversion of the substituent A into the group  $\text{link-P(O)(OR}^1)_2$  are illustrated below, (Schemes 24 -69).

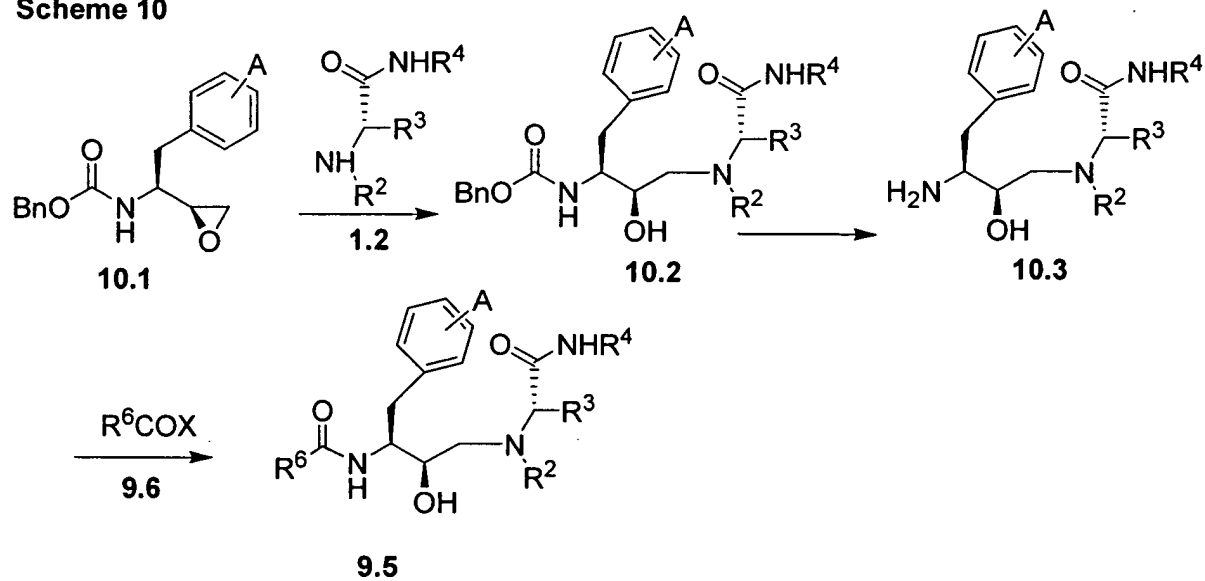
Schemes 12 and 13 depict the preparation of compounds **2** in which X is sulfur. As shown in Scheme 12, a substituted thiophenol **12.2**, in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as [OH], [SH] Br, as described below, is reacted with methanesulfonic acid 2-benzyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester **12.1**, the preparation of which is described in *J. Org. Chem.*, 2000, 65, 1623, to afford the displacement product **12.3**. The conditions for the reaction are the same as described above for the preparation of the thioether **7.3**. Methods for the preparation of the substituted thiophenol **12.2** are described below, Schemes 35 - 44. The thioether product **12.3** is then transformed, using the series of reactions described above, Scheme 7, for the conversion of the thioether **7.3** into the amine **7.9**. The conditions employed for this series of reactions are the same as those described above, (Scheme 7). The amine **12.4** is then reacted with the carboxylic acid or activated derivative thereof, **9.6** to afford the amide **12.5**. The conditions for the reaction are the same as those described above for the preparation of the amide **9.5**.

The procedures illustrated in Scheme 12 depict the preparation of the compounds **12.5** in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 13 illustrates the conversion of compounds **12.5** in which A is a precursor to the group  $\text{link-P(O)(OR}^1)_2$  into the compounds **2**. Procedures for the conversion of the substituent A into the group  $\text{link-P(O)(OR}^1)_2$  are illustrated below, (Schemes 24 - 69).

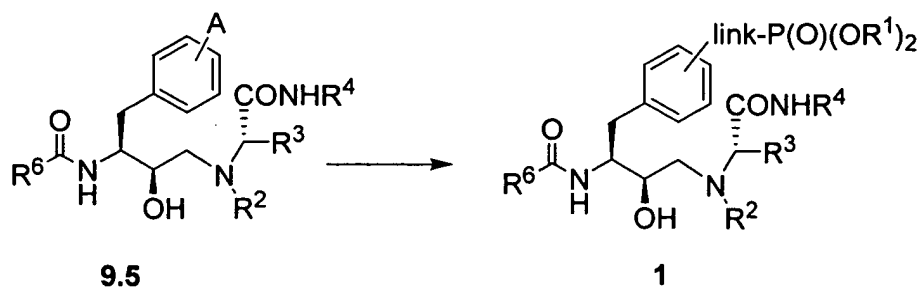
**Scheme 9**



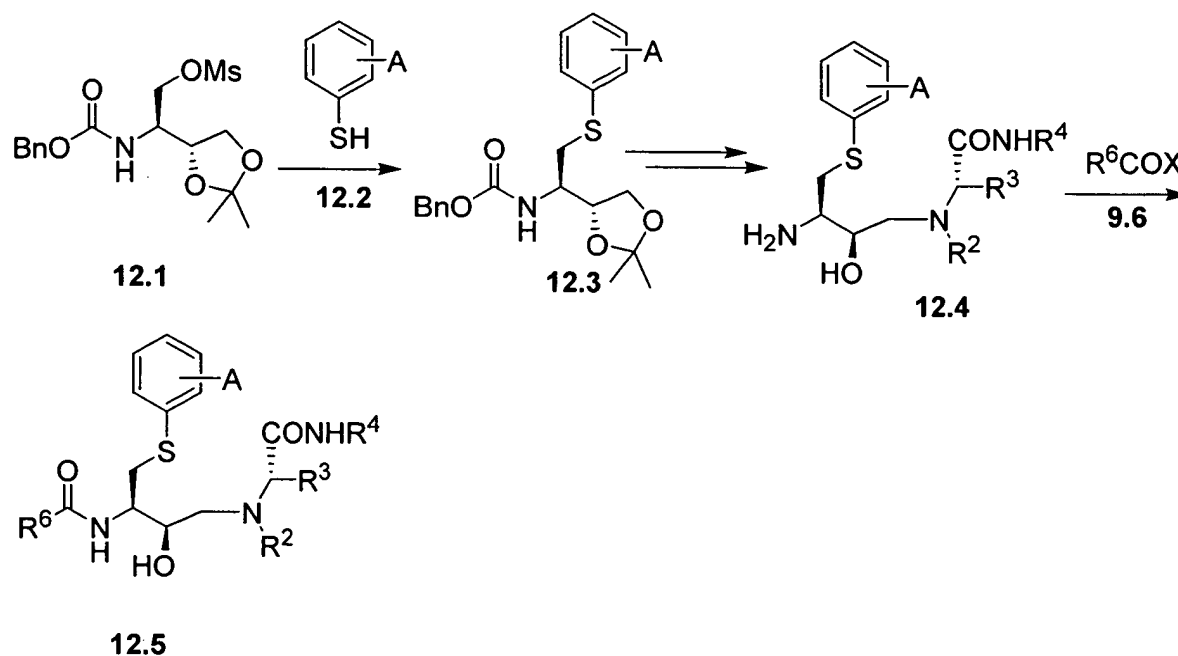
**Scheme 10**



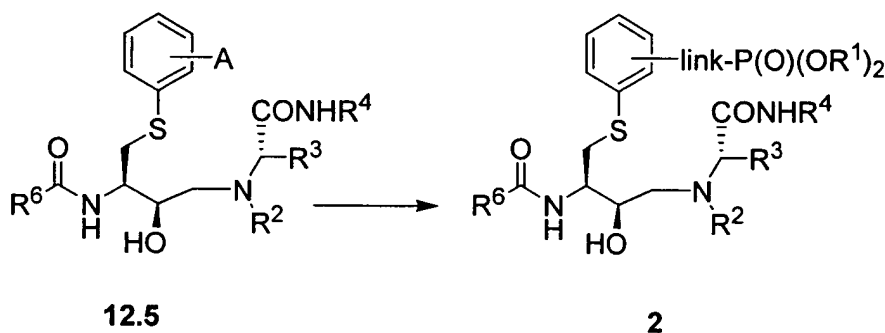
**Scheme 11**



### Scheme 12



### Scheme 13



### Preparation of the phosphonate intermediates 3

Schemes 14-16 depict the preparation of the phosphonate esters 3 in which X is a direct bond. As shown in Scheme 14, the oxirane 1.1, the preparation of which is described above, is reacted with the amine 14.1 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below, to yield the hydroxyamine 14.2. The conditions for the reaction are the same as described above for the preparation of the amine 1.3. Methods for the preparation of the amine 14.1 are described below, Schemes 45 - 48. The hydroxyamine product 14.2 is then deprotected to afford the free amine 14.3. The conditions for the debenzoylation reaction are the same as those described above for the preparation of the amine 1.4. (Scheme 1). The amine 14.3 is then coupled with the carboxylic acid or activated derivative

thereof, **9.6**, to afford the amide **14.4**, using the conditions described above for the preparation of the amide **12.5**.

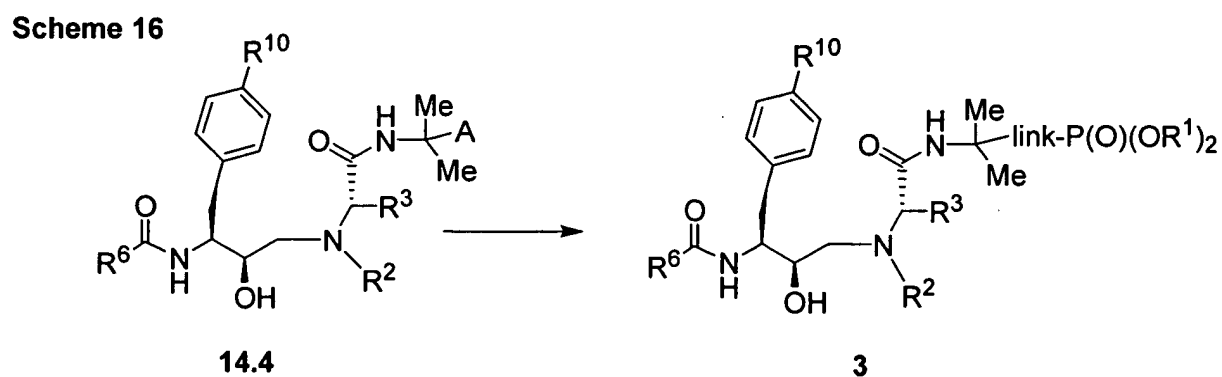
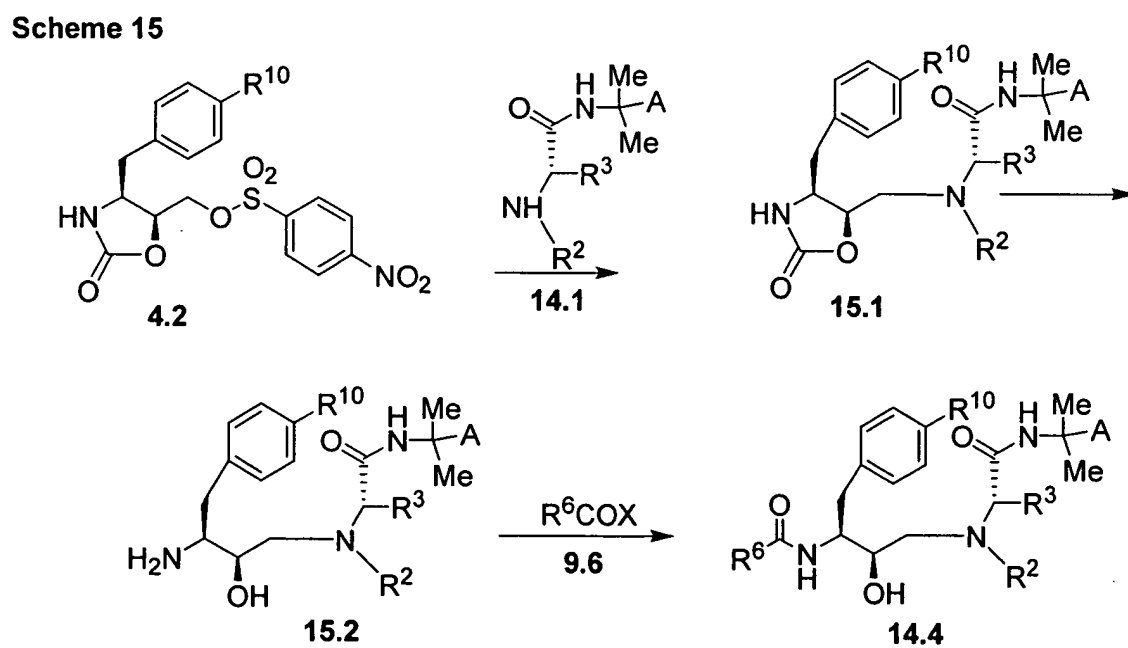
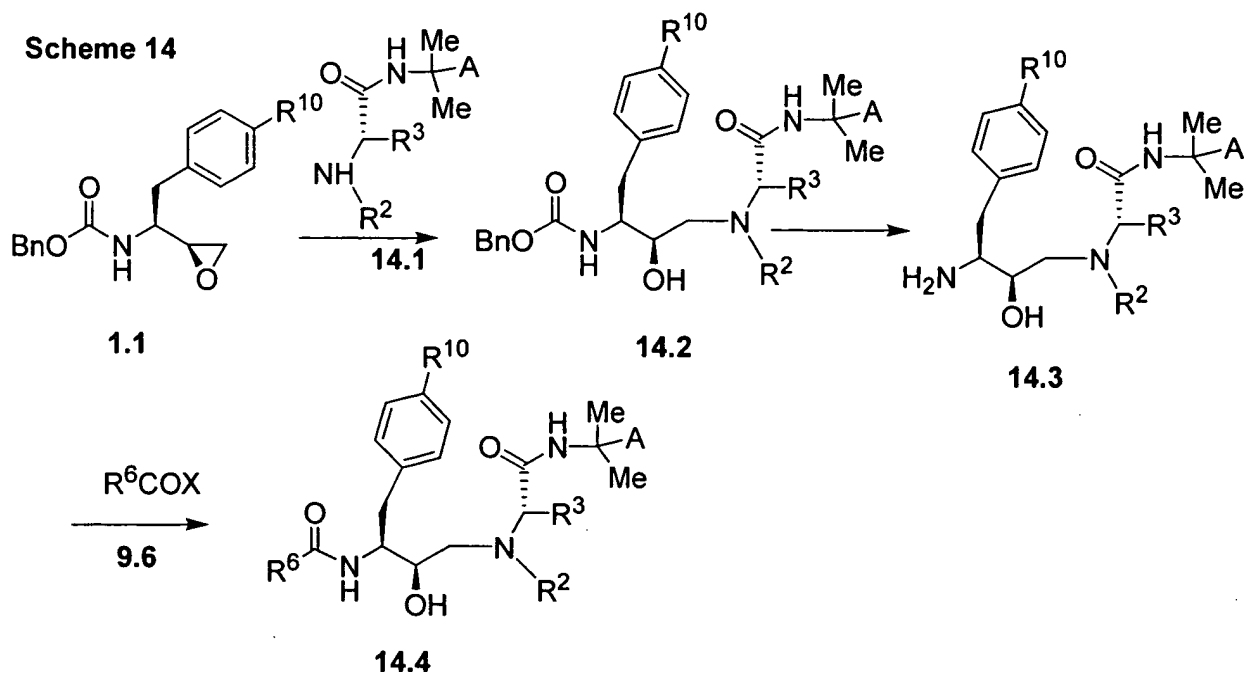
Scheme **15** illustrates an alternative method for the preparation of the phosphonate esters **14.4**. In this reaction sequence, the 4-nitrobenzenesulfonate **4.2**, the preparation of which is described above, (Scheme **4**), is reacted with the amine **14.1**, in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below, to yield the amine **15.1**. The reaction is conducted under the same conditions as described above for the preparation of the amide **4.3**. The oxazolidine moiety present in the product is then removed, using the procedure described above for the conversion of the oxazolidine **4.3** into the hydroxyamine **4.4**, to afford the hydroxyamine **15.2**. The latter compound is then coupled, as described above, with the carboxylic acid or activated derivative thereof, **9.6**, to afford the amide **14.4**.

The procedures illustrated in Schemes **14** and **15** depict the preparation of the compounds **14.4** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **16** illustrates the conversion of compounds **14.4** in which A is a precursor to the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> into the compounds **3**. Procedures for the conversion of the substituent A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> are illustrated below, (Schemes **24 - 69**).

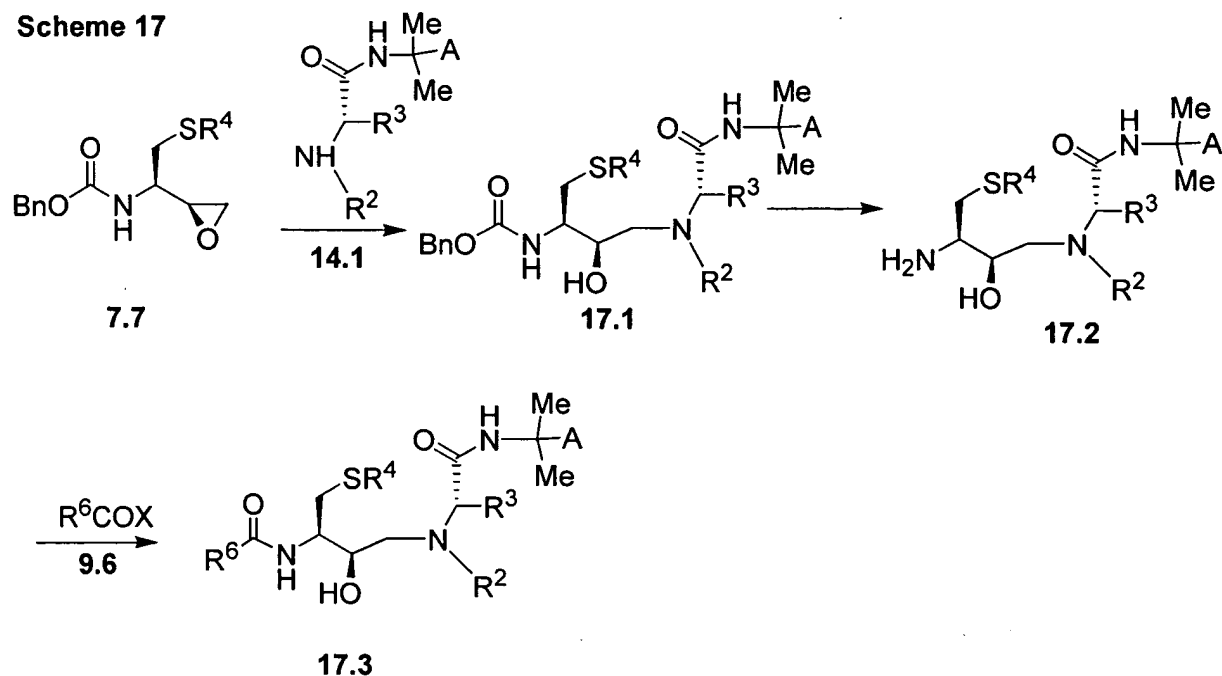
Schemes **17** and **18** illustrate the preparation of the phosphonate esters **3** in which X is sulfur. As shown in Scheme **17**, the oxirane **7.7**, the preparation of which is described above, (Scheme **7**) is reacted with the amine **14.1**. The conditions for the ring-opening reaction are the same as those described above for the preparation of the aminoalcohol **7.8**, (Scheme **7**). The benzyloxycarbonyl protecting group is then removed to produce the free amine **17.2**. The conditions for the deprotection reaction are the same as those described above for the conversion of the protected amine **7.8** to the amine **7.9** (Scheme **7**). The amine product **17.2** is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as described above, to afford the amide **17.3**.

The procedures illustrated in Scheme **17** depict the preparation of the compound **17.3** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **18** illustrates the conversion of compounds **17.3** in which A is a precursor to the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> into the compounds **3**. Procedures for the

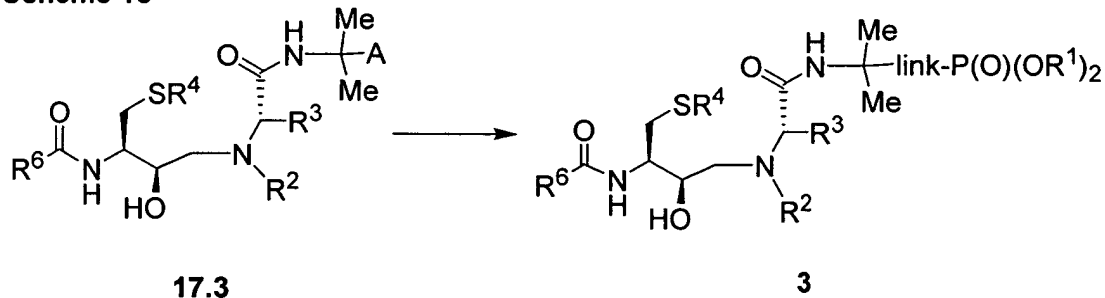
conversion of the substituent A into the group  $\text{link-P(O)(OR}^1\text{)}_2$  are illustrated below, (Schemes 24 - 69).



**Scheme 17**



**Scheme 18**



### Preparation of the phosphonate intermediates 4

Scheme 19 illustrates one method for the preparation of the phosphonate esters 4 in which X is a direct bond. In this reaction sequence, the oxirane 1.1, the preparation of which is described above (Scheme 2) is reacted with the decahydroisoquinoline amine 19.1, in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as [OH], [SH] Br, as described below, to afford the aminoalcohol product 19.2. The conditions for the ring-opening reaction are the same as those described above for the preparation of the aminoalcohol 1.3. The preparation of the decahydroisoquinoline derivatives 19.1 is described below, (Schemes 48a - 52). The cbz protecting group is then removed to yield the free amine 19.3, using the same conditions as described above for the preparation of the amine 1.4, (Scheme 1). The amine 19.3

is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as described above, to afford the amide **19.4**.

Scheme **20** illustrates an alternative method for the preparation of the phosphonate intermediates **19.4**. In this procedure, the 4-nitrobenzenesulfonyl ester **4.2**, the preparation of which is described above, (Scheme **4**) is reacted with the decahydroisoquinoline derivative **20.1**, in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as [OH], [SH] Br, as described below. The reaction conditions for the displacement reaction are the same as those described above for the preparation of the amine **4.3**, (Scheme **4**). The oxazolidinone moiety present in the product **20.2** is then hydrolyzed, using the procedures described above (Scheme **4**) to afford the free amine **20.3**. This compound is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as are described above, to afford the amide product **19.4**.

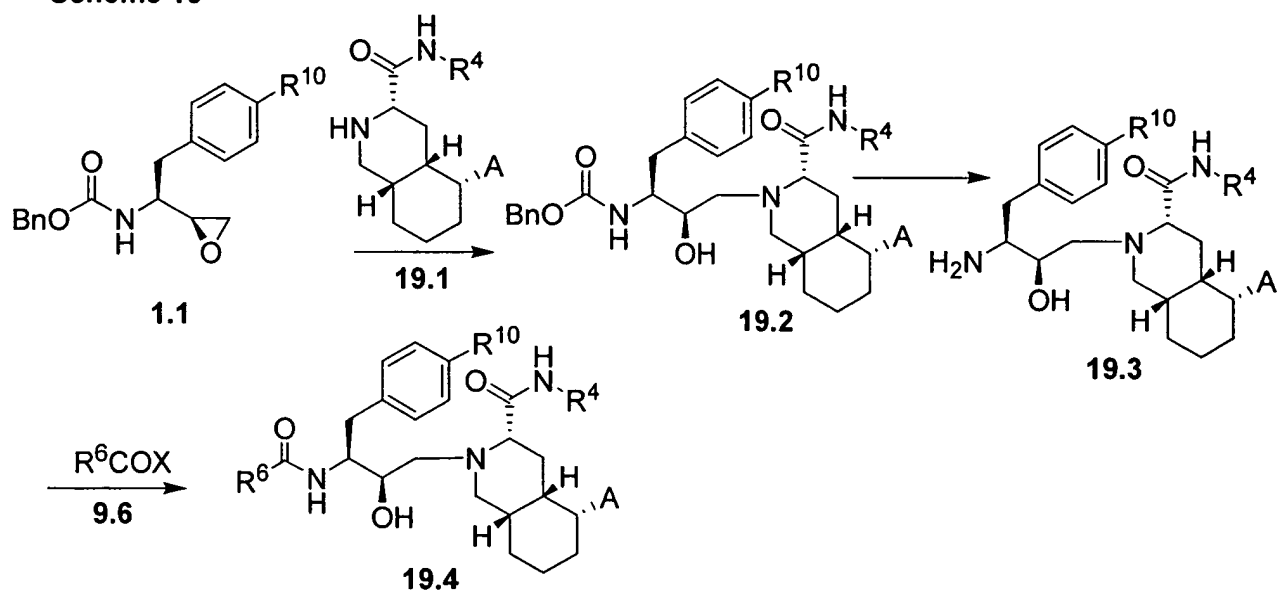
The procedures illustrated in Schemes **19** and **20** depict the preparation of the compounds **19.4** in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **21** illustrates the conversion of compounds **19.4** in which A is a precursor to the group  $\text{link-P(O)(OR}^1)_2$  into the compounds **4**. Procedures for the conversion of the substituent A into the group  $\text{link-P(O)(OR}^1)_2$  are illustrated below, (Schemes **24 - 69**).

Schemes **22** and **23** depict the preparation of the phosphonate esters **4** in which X is sulfur. As shown in Scheme **22**, the oxirane **7.7**, prepared as described above (Scheme **7**) is reacted with the decahydroisoquinoline derivative **19.1**, in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as [OH], [SH] Br, as described below. The reaction is conducted under the same conditions as described above for the preparation of the amine **7.8**, (Scheme **7**), to produce the hydroxyamine **22.1**. The cbz protecting group present in the product **22.1** is then removed, using the same procedures as described above (Scheme **7**) to afford the free amine **22.2**. This material is then coupled with the carboxylic acid or activated derivative thereof, **9.6** to yield the amide **22.3**. The coupling reaction is preformed under the same conditions as previously described.

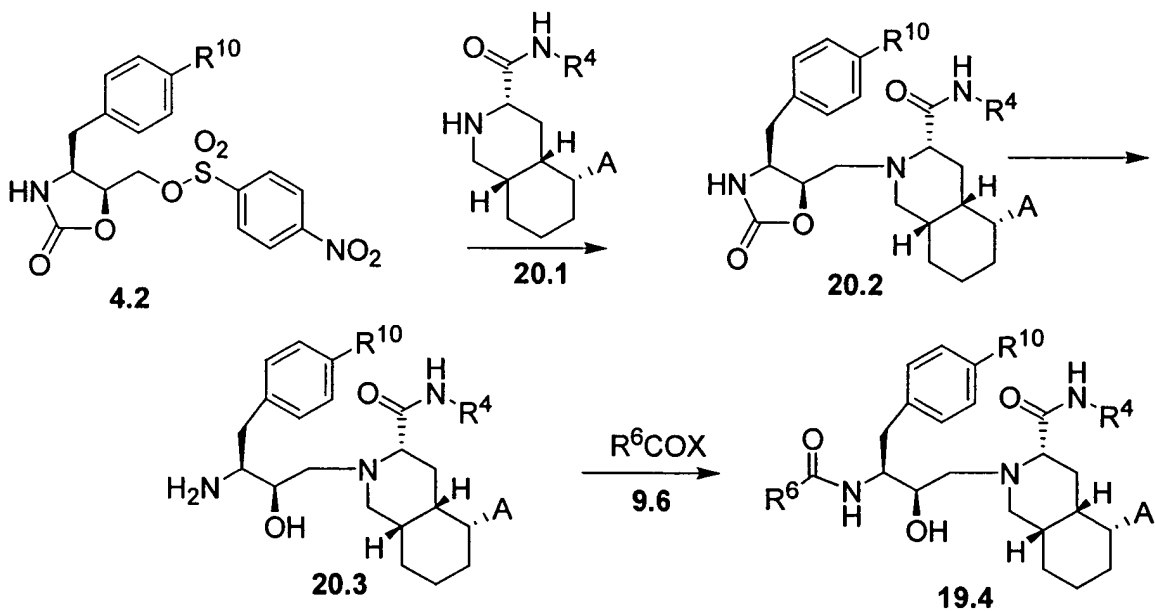
The procedures illustrated in Scheme **22** depict the preparation of the compounds **22.3** in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **23** illustrates the conversion of compounds **22.3** in which

A is a precursor to the group  $\text{link-P(O)(OR}^1\text{)}_2$  into the compounds **4**. Procedures for the conversion of the substituent A into the group  $\text{link-P(O)(OR}^1\text{)}_2$  are illustrated below, (Schemes **24 - 69**).

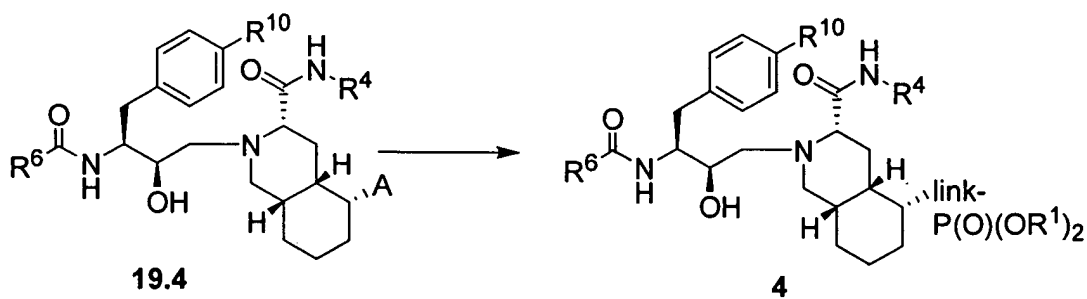
### Scheme 19



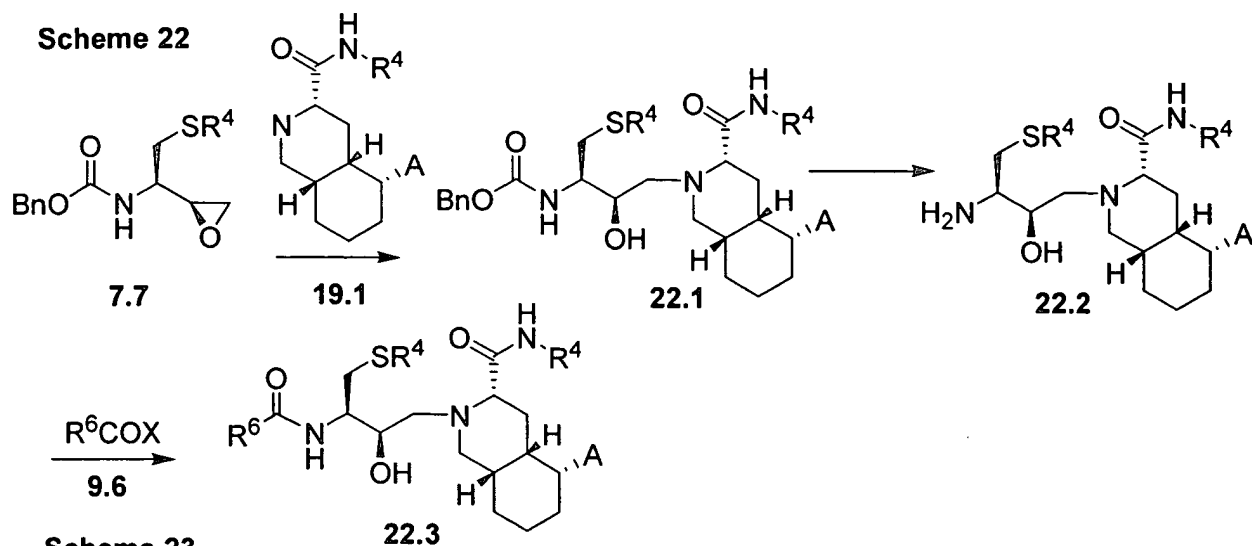
### Scheme 20



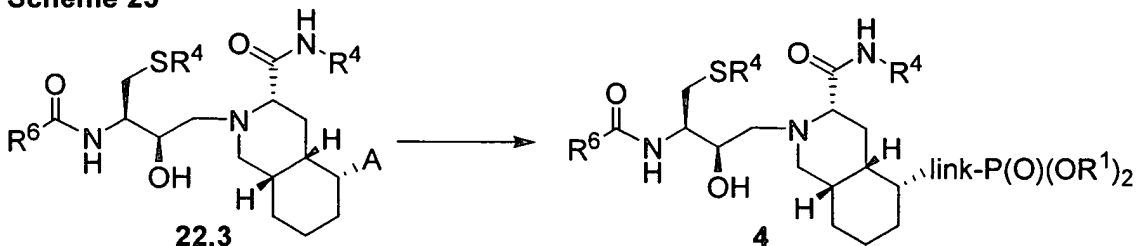
### Scheme 21



**Scheme 22**

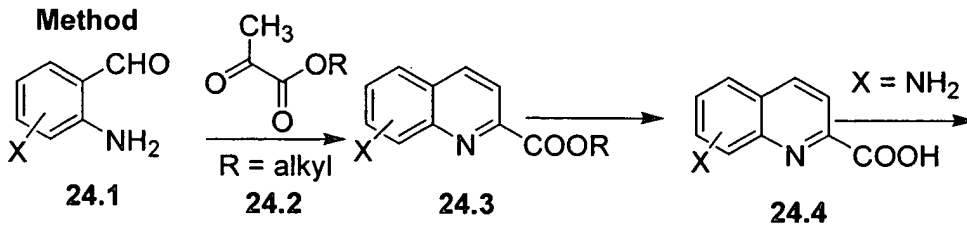


**Scheme 23**

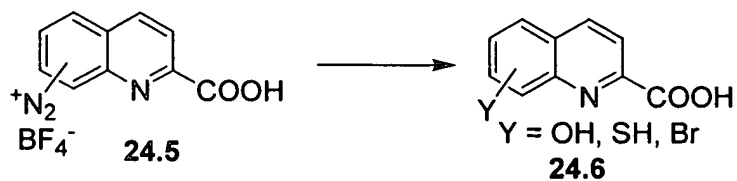


**Scheme 24**

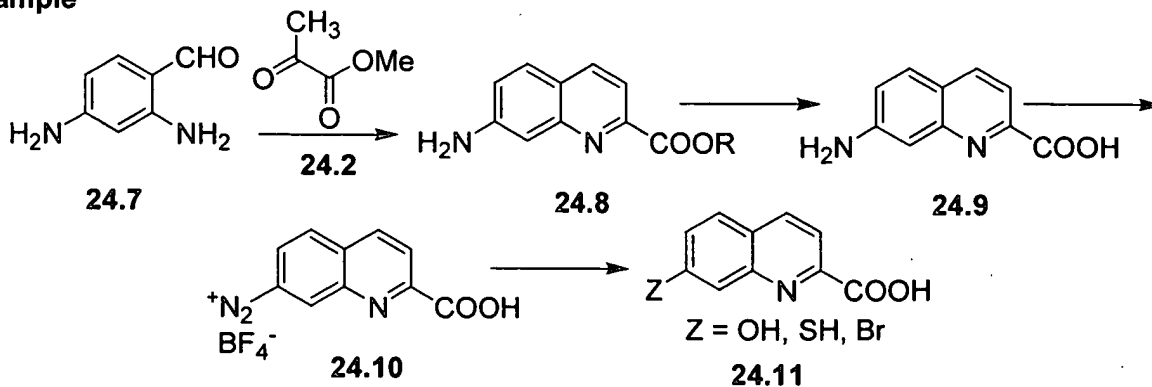
**Method**



X = OH, SH, NH<sub>2</sub>, Br



**Example**



### Preparation of quinoline 2-carboxylic acids 1.7 incorporating phosphonate moieties or precursors thereto

The reaction sequence depicted in Scheme 1 requires the use of a quinoline-2-carboxylic acid reactant 1.7 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, *J. Het. Chem.*, 1989, 26, 929 and *J. Labelled Comp. Radiopharm.*, 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in *J. Am. Chem. Soc.*, 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p. 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme 24 illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde 24.1 is reacted with an alkyl pyruvate ester 24.2, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester 24.3. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid 24.4. The carboxylic acid product 24.4 in which X is NH<sub>2</sub> can be further transformed into the corresponding compounds 24.6 in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in *Sulfur Lett.*, 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol 24.6, X = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous

bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **24.6**, Y = Br. Alternatively, the diazonium tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in *Sulfur Lett.*, 200, 24, 123, to afford the thiol **24.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **24.3** instead of the carboxylic acids **24.5**.

For example, 2,4-diaminobenzaldehyde **24.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **24.2** in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **24.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **24.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoborate **24.10** by reaction with sodium nitrite and tetrafluoroboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **24.11**, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **24.11**, X = Br. Alternatively, the diazonium tetrafluoborate **24.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in *Sulfur Lett.*, 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **24.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **24.7**, different aminobenzaldehydes **24.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **24.6** are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described below, (Schemes 25 – 27) into phosphonate-containing derivatives.

Scheme 25 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **25.1** is transformed, via a diazotization procedure as described above (Scheme 24) into the corresponding phenol or thiol **25.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate **25.3**, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester **25.4**. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced

Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the thioether products **25.5**. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **25.6**.

For example, methyl 6-amino-2-quinoline carboxylate **25.7**, prepared as described in *J. Het. Chem.*, 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate **25.8**. This material is reacted with a dialkyl hydroxymethylphosphonate **25.9** (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether **25.10**. Basic hydrolysis then afford the carboxylic acid **25.11**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate **25.7**, different aminoquinoline carboxylic esters **25.1**, and/or different dialkyl hydroxymethylphosphonates **25.9** the corresponding phosphonate ester products **25.3** are obtained.

Scheme 26 illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **26.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate **26.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound **26.1** and the olefin **26.2** affords the olefinic ester **26.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid **26.4**. Optionally, the unsaturated carboxylic acid **26.4** can be reduced to afford the saturated analog **26.5**. The reduction reaction can be effected chemically, for example by the

use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5.

For example, methyl 7-bromoquinoline-2-carboxylate, **26.6**, prepared as described in *J. Labelled Comp. Radiopharm.*, 1998, 41, 1103, is reacted in dimethylformamide at 60°C with a dialkyl vinylphosphonate **26.7** (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **26.8**. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid **26.9**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in *Angew. Chem. Int. Ed.*, 4, 271, 1965, to yield the saturated product **26.10**.

Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **26.6**, different bromoquinoline carboxylic esters **26.1**, and/or different dialkyl alkenylphosphonates **26.2**, the corresponding phosphonate ester products **26.4** and **26.5** are obtained.

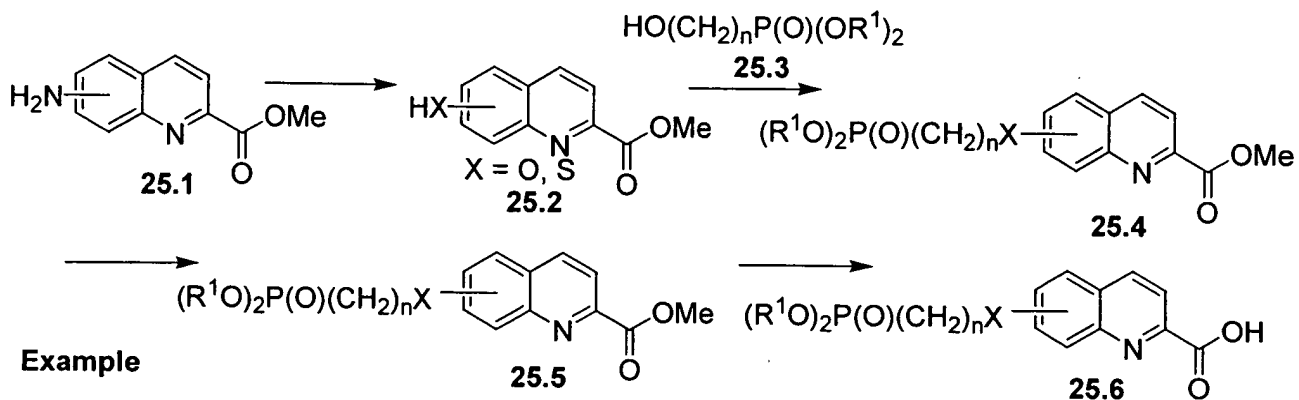
Scheme 27 depicts the preparation of quinoline-2-carboxylic acids **27.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **27.1** is reacted with a phosphonate aldehyde **27.2** under reductive amination conditions, to afford the aminoalkyl product **27.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The ester product **27.4** is then hydrolyzed to yield the free carboxylic acid **27.5**.

For example, methyl 7-aminoquinoline-2-carboxylate **27.6**, prepared as described in *J. Amer. Chem. Soc.*, 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **27.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **27.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **27.9**.

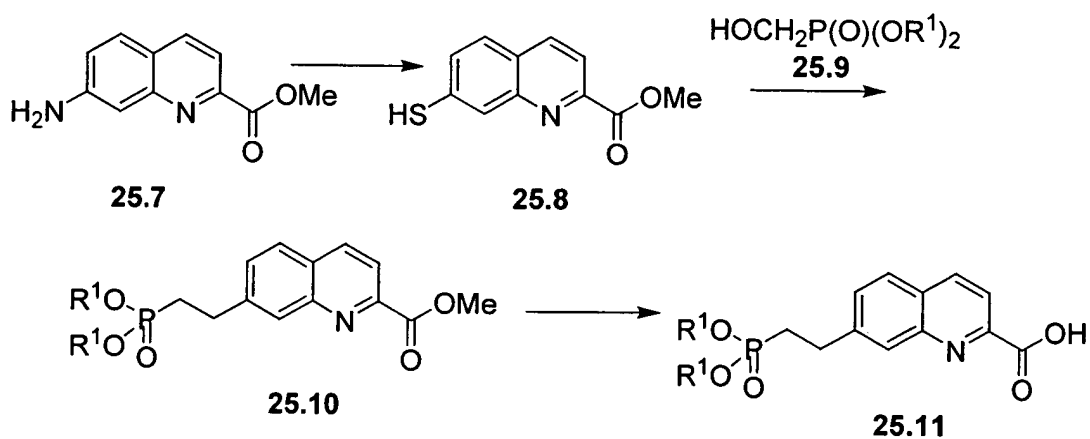
Using the above procedures, but employing, in place of the formylmethyl phosphonate 27.2, different formylalkyl phosphonates, and/or different aminoquinolines 27.1, the corresponding products 27.5 are obtained.

#### Scheme 25

##### Method

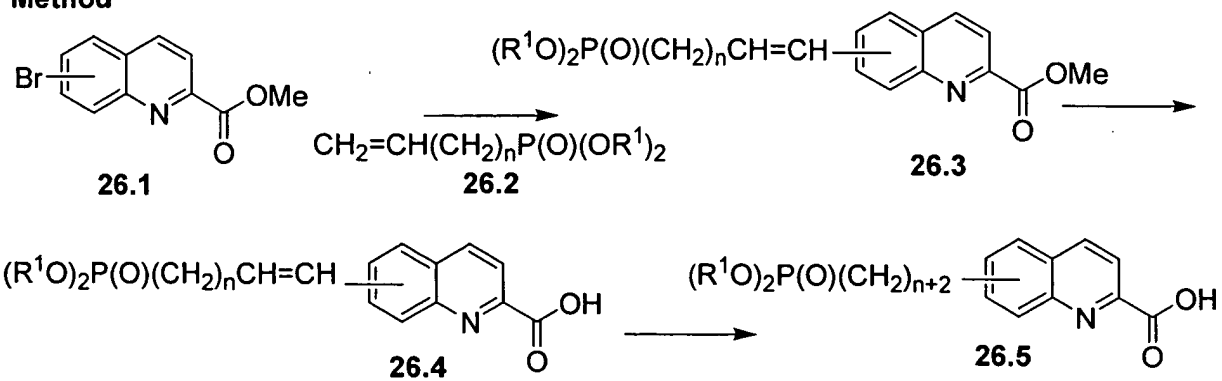


##### Example

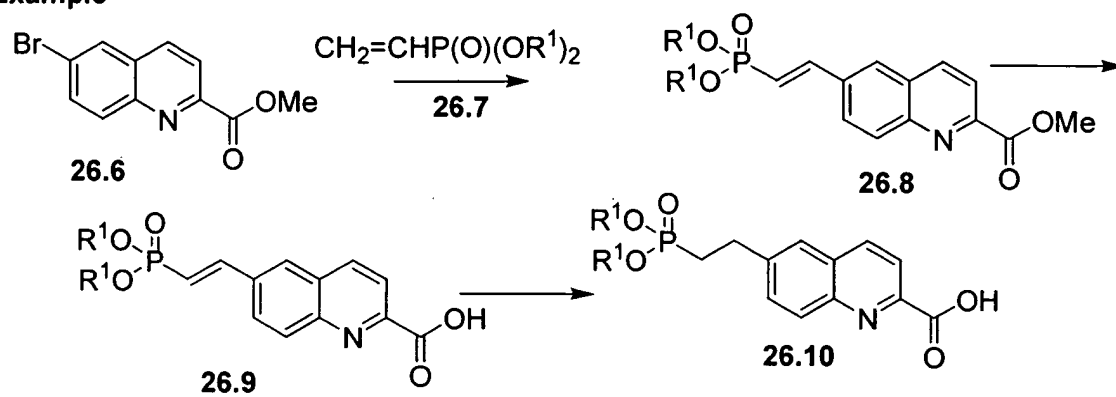


## Scheme 26

### Method

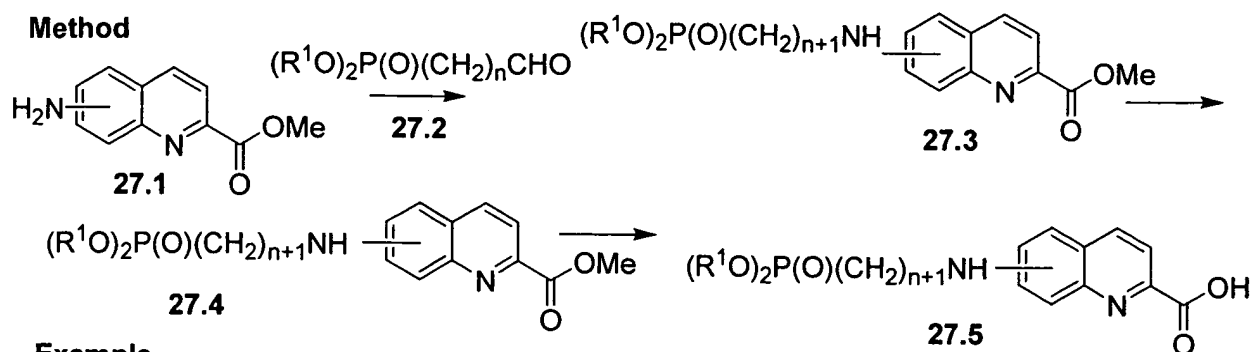


### Example

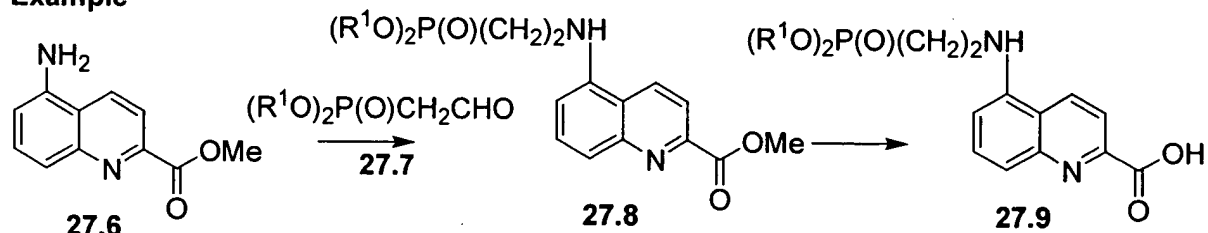


### Scheme 27

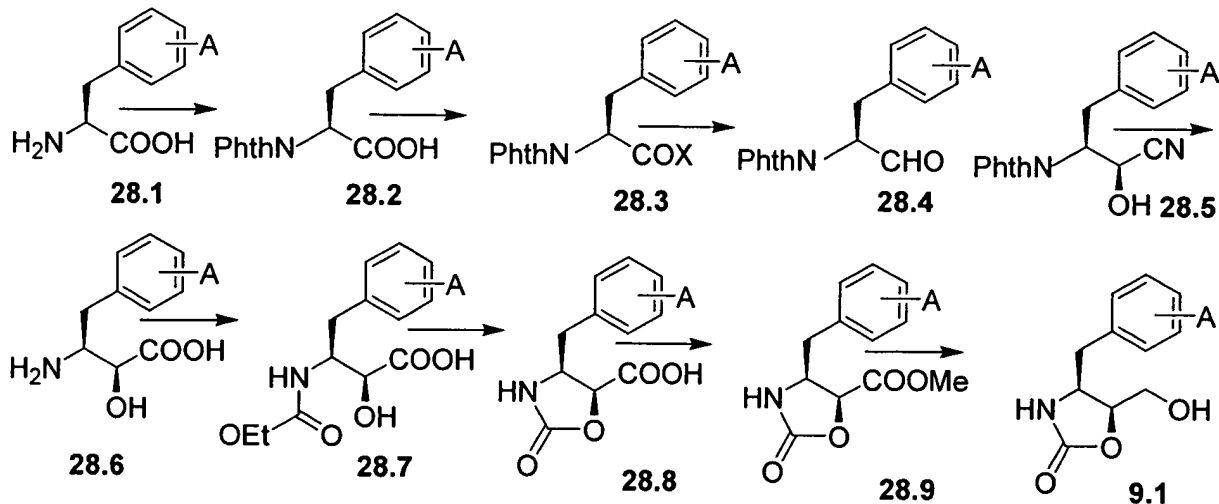
#### Method



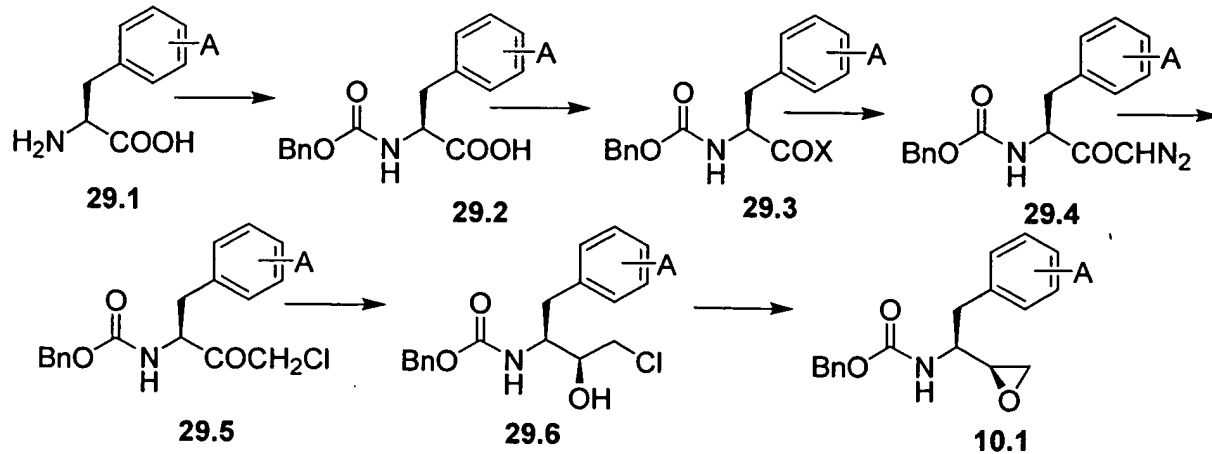
#### Example



### Scheme 28



### Scheme 29



## Preparation of phenylalanine derivatives 9.1 and 10.1 incorporating phosphonate moieties or precursors thereto

Scheme 28 illustrates the preparation of the hydroxymethyl oxazolidine derivative **9.1**, in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br. In this reaction sequence, the substituted phenylalanine **28.1**, in which A is as defined above, is transformed, via the intermediates **28.2-28.9**, into the hydroxymethyl product **9.1**. The reaction conditions for each step in the sequence are the same as those described above for the corresponding step shown in Scheme 5. The conversion of the substituent A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> may be effected at any convenient step in the reaction sequence, or after the reactant **9.1** has been incorporated into the intermediates **9.5** (Scheme 9). Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant **9.1** are shown below, (Schemes 30-31).

Scheme 29 illustrates the preparation of the oxirane intermediate **10.1**, in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as [OH], [SH] Br. In this reaction sequence, the substituted phenylalanine **29.1**, in which A is as defined above, is transformed, via the intermediates **29.2-29.6**, into the oxirane **10.1**. The reaction conditions for each step in the sequence are the same as those described above for the corresponding step shown in Scheme 2. The conversion of the substituent A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> may be effected at any convenient step in the reaction sequence, or after the reactant **10.1** has been incorporated into the intermediates **9.5** (Scheme 10). Specific examples of the preparation of the oxiranes reactant **10.1** are shown below, (Schemes 32-34).

Scheme 30 depicts the preparation of hydroxymethyloxazolidinones **30.9** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **30.1** is converted, using the series of reactions illustrated in Scheme 28, into the bromophenyloxazolidinone **30.2**. The bromophenyl compound is then coupled, in the presence of a palladium (0) catalyst, with a dialkyl phosphite **30.3**, to afford the phosphonate product **30.4**. The reaction between aryl bromide and dialkyl phosphites to yield aryl phosphonates is described in *Synthesis*, 56, 1981, and in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester **30.4** is then reduced with sodium borohydride to the corresponding hydroxymethyl derivative **30.5**, using the procedure described above (Scheme 28)

For example, 3-bromophenylalanine **30.6**, prepared as described in *Pept. Res.*, 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme 28, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester **30.7**. This compound is then coupled with a dialkyl phosphite **30.3**, in toluene solution at reflux, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester **30.8**. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product **30.9**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **30.6** different bromophenylalanines **30.1** and/or different dialkyl phosphites **30.3**, the corresponding products **30.5** are obtained.

Scheme 31 illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones **31.9** and **31.12** in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted phenylalanine **31.1** is converted into the benzyl ester **31.2** by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in *Bull. Chem. Soc. Jpn.*, 37, 433, 1974. The protected ester **31.3** is then reacted with phthalic anhydride, as described above (Scheme 28) to afford the phthalimide **31.4**. The benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid **31.5**. This compound is transformed, by means of the series of reactions shown in Scheme 28, into the carbomethoxy oxazolidinone **31.6**, using in each step the same conditions as are described above (Scheme 28). The protected OH or SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis,

by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in *J. Am Chem. Soc.*, 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in *Chem. Pharm. Bull.*, 26, 1576, 1978. The resultant phenol or thiol **31.7** is then reacted with a hydroxyalkyl phosphonate **31.20** under the conditions of the Mitsunobu reaction, as described above (Scheme 25), to afford the ether or thioether **31.8**. The latter compound is then reduced with sodium borohydride, as described above (Scheme 28) to afford the hydroxymethyl analog **31.9**.

Alternatively, the phenol or thiophenol **31.7** is reacted with a dialkyl bromoalkyl phosphonate **31.10** to afford the alkylation product **31.11**. The alkylation reaction is preformed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound **31.12**.

For example, 3-hydroxyphenylalanine **31.13** (Fluka) is converted in to the benzyl ester **31.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **31.15**. The protected ether is then reacted with phthalic anhydride, as described above (Scheme 28) to yield the phthalimido-protected compound **31.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **31.17**. This compound is then transformed, by means of the series of reactions shown in Scheme 28, into the carbomethoxy-substituted oxazolidinone **31.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, to produce the phenol **31.19**. The latter compound is reacted with a dialkyl hydroxymethyl phosphonate **31.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsunobu reaction, as described above (Scheme 25) to yield the phenolic ether **31.21**. The carbomethoxy group is then reduced by reaction with sodium borohydride, as described above, to afford the carbinol **31.22**.

Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **31.13**, different hydroxy or mercapto-substituted phenylalanines **31.1**, and/or different dialkyl hydroxyalkyl phosphonates **31.20**, the corresponding products **31.9** are obtained.

As a further example of the methods illustrated in Scheme **31**, 4-mercaptophenylalanine **31.23**, prepared as described in *J. Amer. Chem. Soc.*, 1997, 119, 7173, is converted into the benzyl ester **31.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in *Chem. Pharm. Bull.*, 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic acid **31.27**. The latter compound is then transformed, by means of the series of reactions shown in Scheme **28**, into the carbomethoxy oxazolidinone **31.28**. The adamantyl protecting group is then removed by treatment of the thioether **31.28** with mercuric acetate in trifluoroacetic acid at 0°C, as described in *Chem. Pharm. Bull.*, 26, 1576, 1978, to produce the thiol **31.29**. The thiol is then reacted with one molar equivalent of a dialkyl bromoethylphosphonate **31.30**, (Aldrich) and cesium carbonate in dimethylformamide at 70°C, to afford the thioether product **31.31**. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol **31.32**.

Using the above procedures, but employing, in place of 4-mercaptophenylalanine **31.23**, different hydroxy or mercapto-substituted phenylalanines **31.10**, and/or different dialkyl bromoalkyl phosphonates **31.10**, the corresponding products **31.12** are obtained.

Scheme **32** illustrates the preparation of phenylalanine derivatives **32.3** in which the phosphonate group is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **32.1** is converted, by means of the series of reactions shown in Scheme **29** into the oxirane **32.2**. This compound is then coupled with a dialkyl phosphite **30.3**, in the presence of a palladium(0) catalyst and an organic base, to afford the phosphonate oxirane **32.3**. The coupling reaction is performed under the same conditions previously described, (Scheme **30**).

For example, 3-bromophenylalanine **32.4**, prepared as described in *Pept. Res.*, 1990, 3, 176, is converted, as described above, into the oxirane **32.5**. This compound is reacted, in toluene solution at reflux temperature, with a dialkyl phosphonate **30.3**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine to afford the phosphonate ester **32.6**.

Using the above procedures, but employing, in place of 4-bromophenylalanine **32.4**, different bromo-substituted phenylalanines **32.1**, and/or different dialkyl phosphites **30.3**, the corresponding products **32.3** are obtained.

Scheme 33 depicts the preparation of compounds **33.4** in which the phosphonate group is attached to the phenyl ring by means of a styrene moiety. In this reaction sequence, a vinyl-substituted phenylalanine **33.1** is converted, by means of the series of reactions shown in Scheme 29, into the oxirane **33.2**. This compound is then coupled with a dialkyl bromophenylphosphonate **33.3**, employing the conditions of the Heck reaction, as described above (Scheme 26) to afford the coupled product **33.4**.

For example, 4-vinylphenylalanine **33.5**, prepared as described in EP 206460, is converted, as described above, into the oxirane **33.6**. This compound is then coupled with a dialkyl 4-bromophenylphosphonate **33.7**, prepared as described in *J. Chem. Soc. Perkin Trans.*, 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, to yield the phosphonate ester **33.8**.

Using the above procedures, but employing, in place of 4-vinylphenylalanine **33.5**, different vinyl-substituted phenylalanines **33.1**, and/or different dialkyl bromophenylphosphonates **33.3**, the corresponding products **33.4** are obtained.

Scheme 34 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom. In this procedure, a hydroxymethyl-substituted phenylalanine **34.1** is converted into the cbz protected methyl ester **34.2**, using the procedures described above (Scheme 29). The product **34.2** is then converted into a halomethyl-substituted compound **34.3**. For example, the carbinol **34.2** is treated with triphenylphosphine and carbon tetrabromide, as described in *J. Amer. Chem. Soc.*, 108, 1035, 1986 to afford the product **34.3** in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate **34.4**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH<sub>2</sub> or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **34.5**, which is

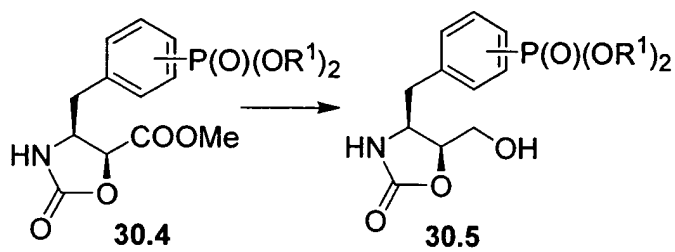
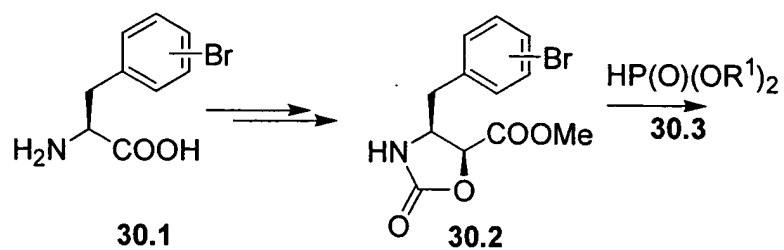
hydrolyzed to afford the carboxylic acid **34.6**. The latter compound is then, by means of the sequence of reactions shown in Scheme 29, is transformed into the epoxide **34.7**.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative **34.9**, obtained from the 4-hydroxymethyl phenylalanine **34.8**, the preparation of which is described in *Syn. Comm.*, 1998, 28, 4279, is converted into the bromo derivative **34.10**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **34.11**, the preparation of which is described in *J. Org. Chem.*, 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **34.12**. The latter compound is then converted, using the sequence of reactions shown in Scheme 29, into the epoxide **34.14**.

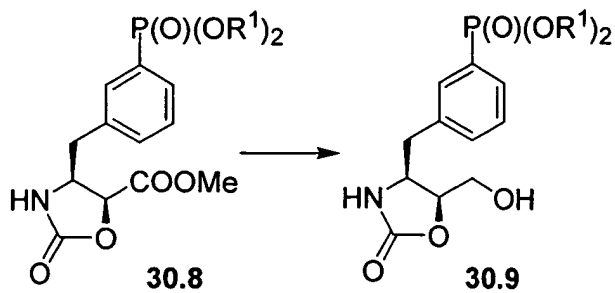
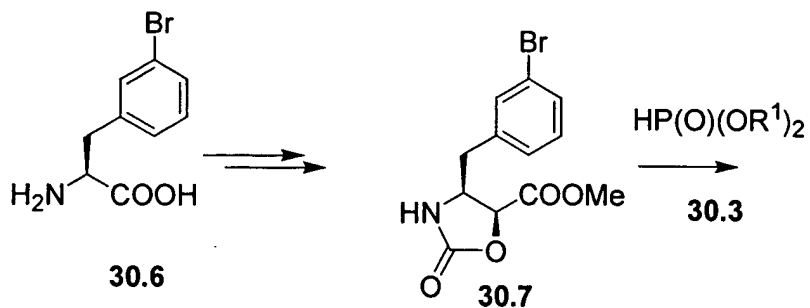
Using the above procedures, but employing different carbinols **34.1** in place of the carbinol **34.8**, and/or different phosphonates **34.4**, the corresponding products **34.7** are obtained.

## Scheme 30

### Method

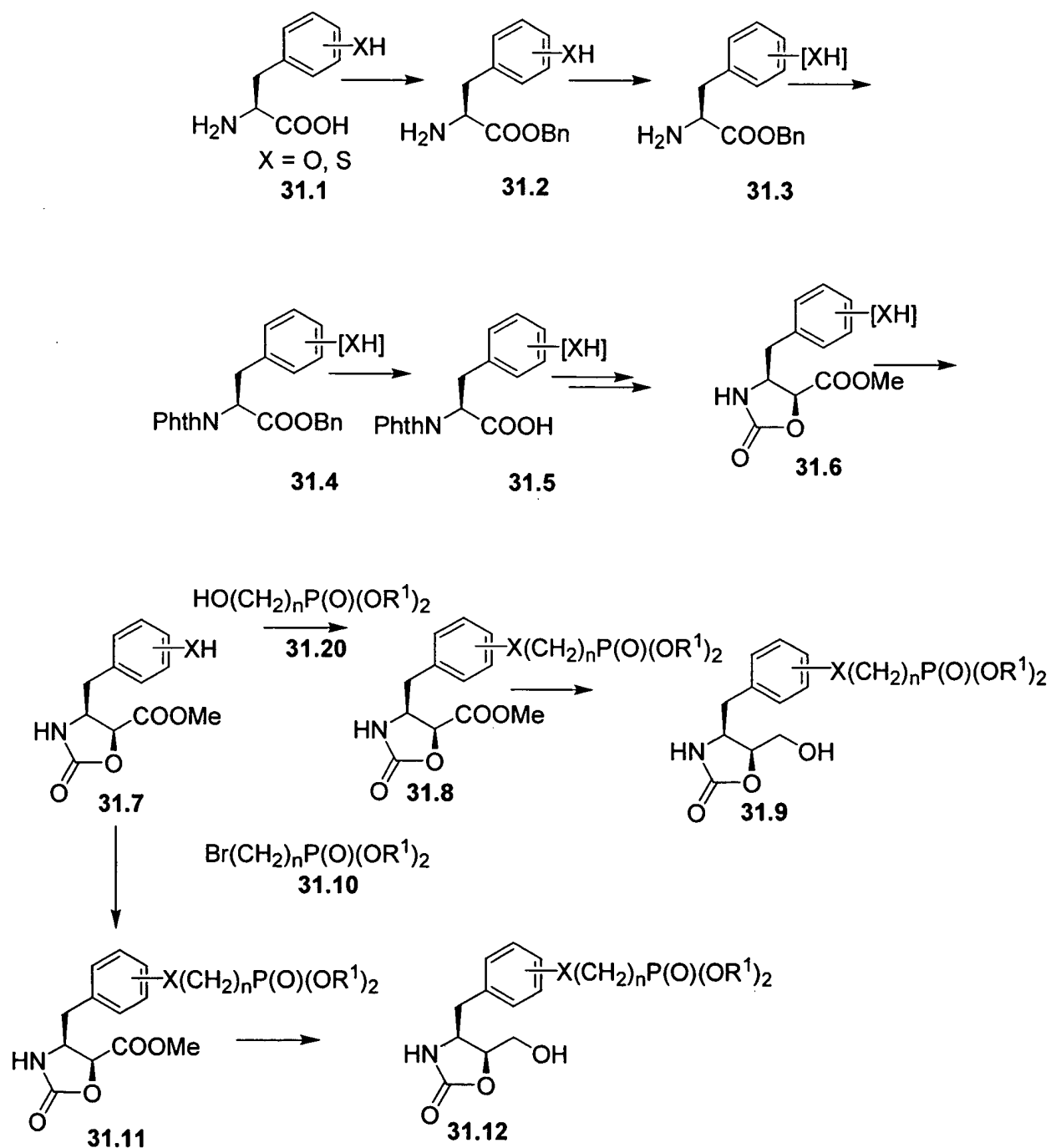


### Example

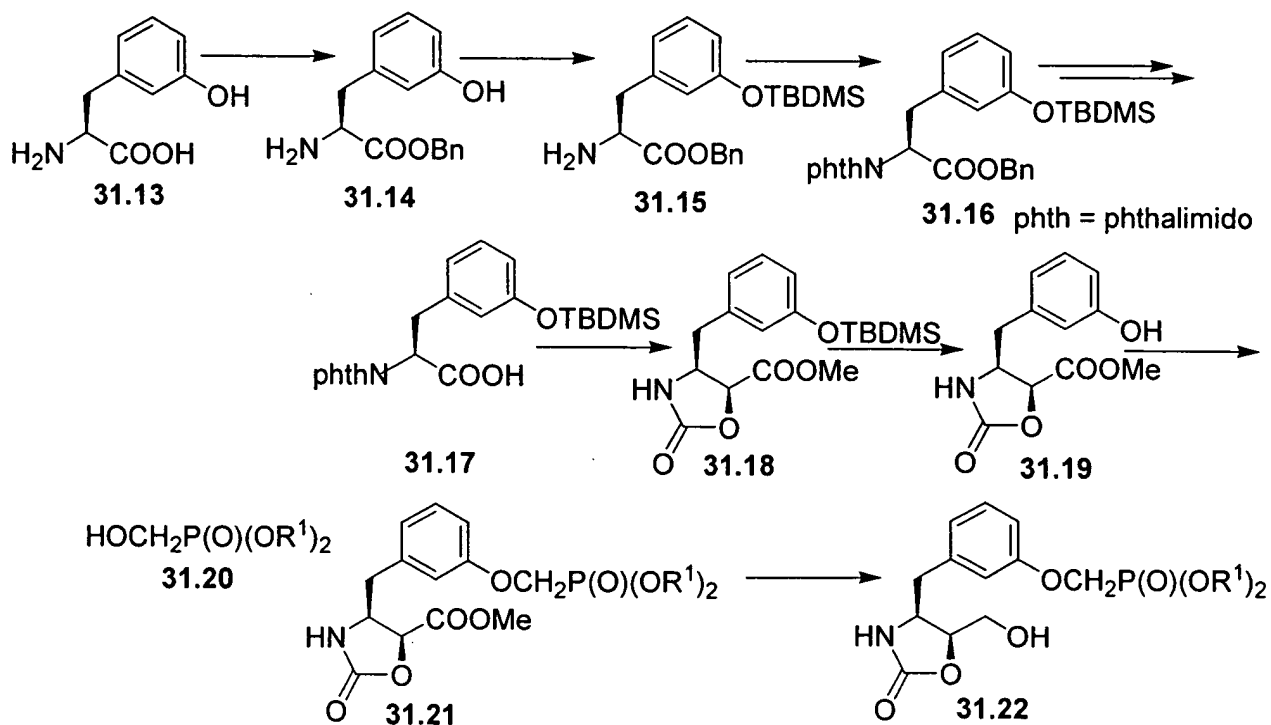


# Scheme 31

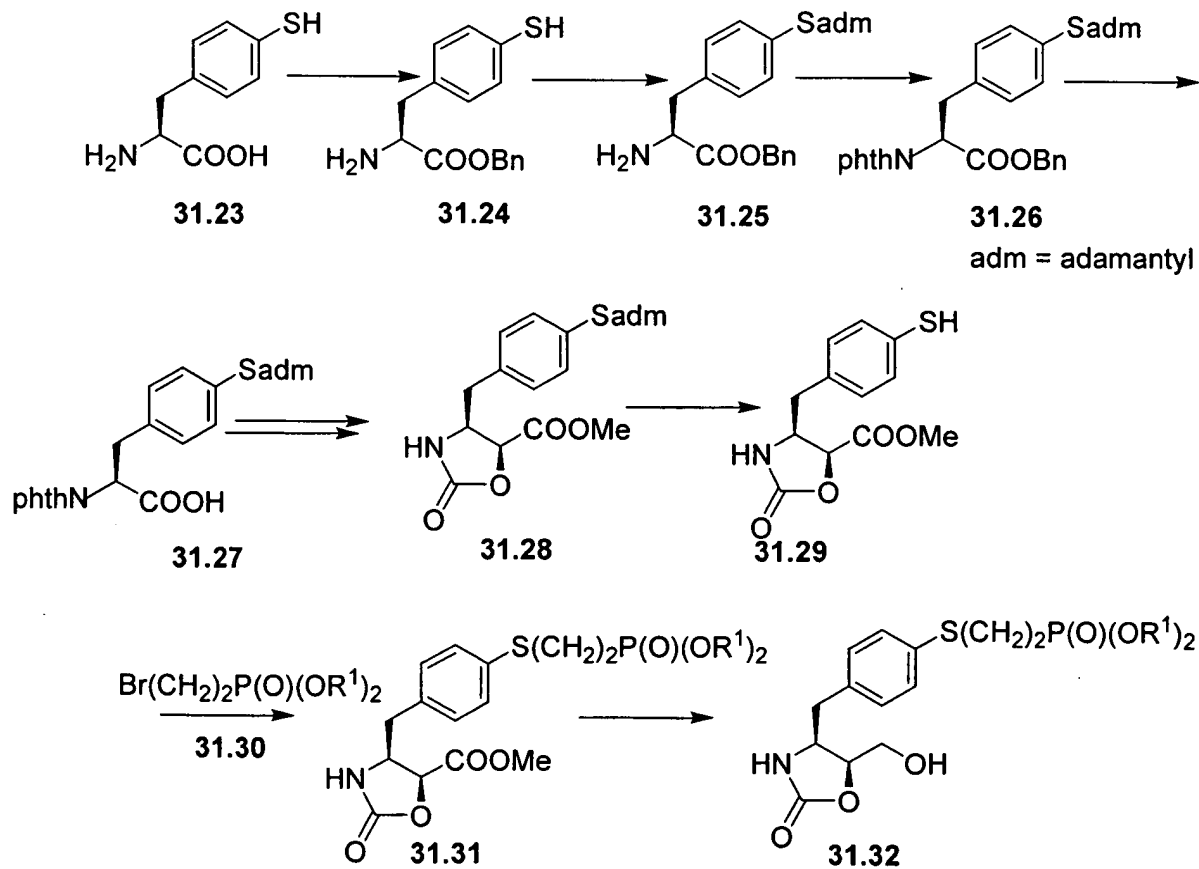
## Method



**Scheme 31 Example 1**

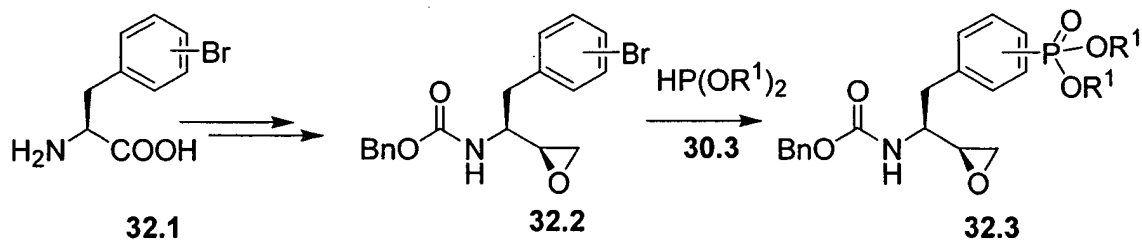


**Scheme 31 Example 2**

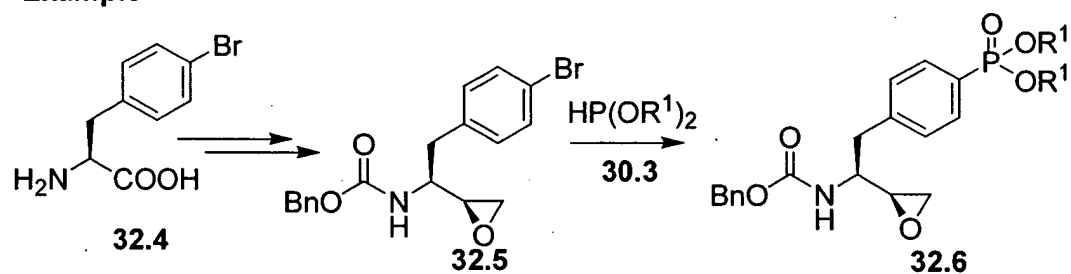


## Scheme 32

### Method

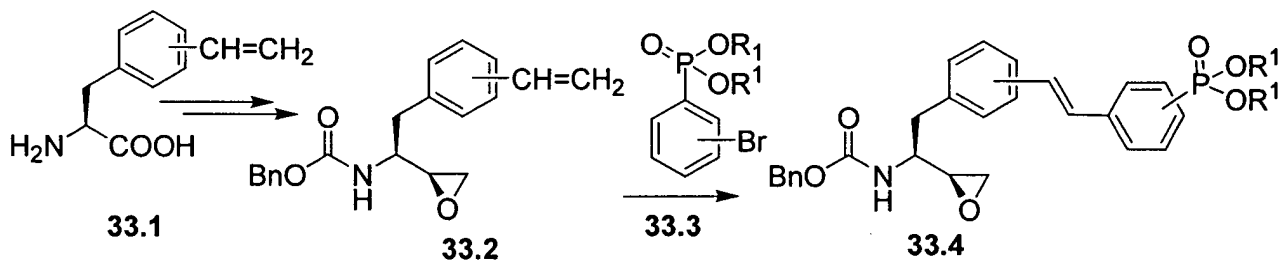


### Example

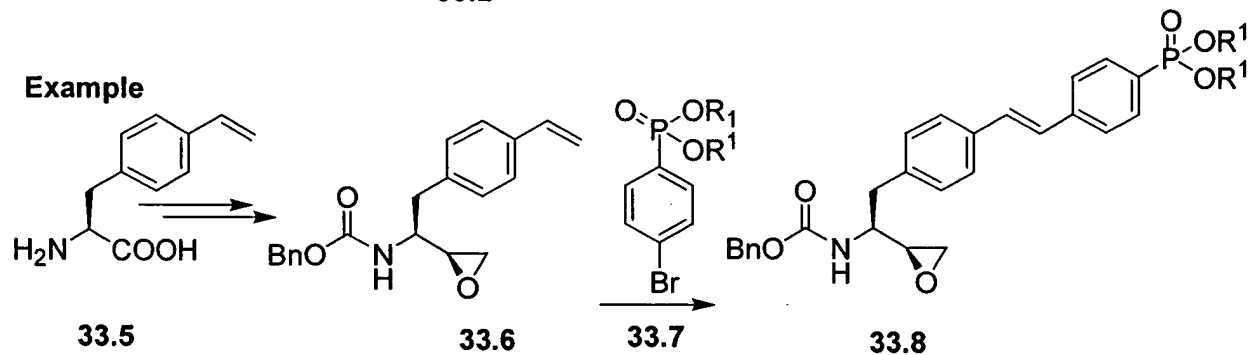


## Scheme 33

### Method

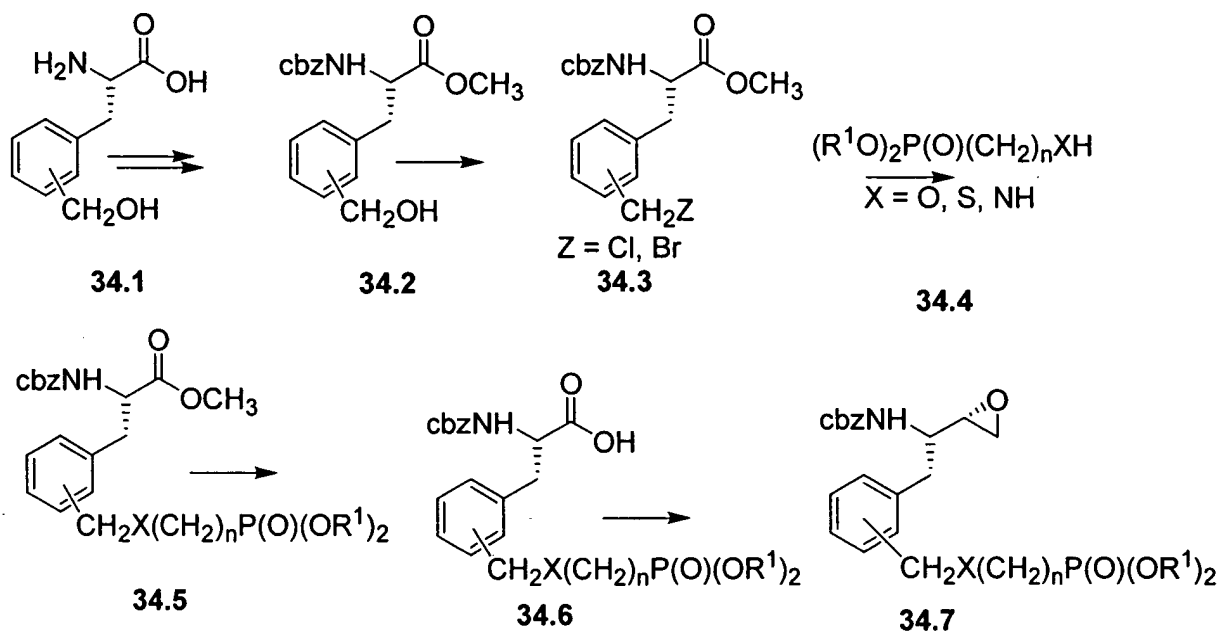


### Example

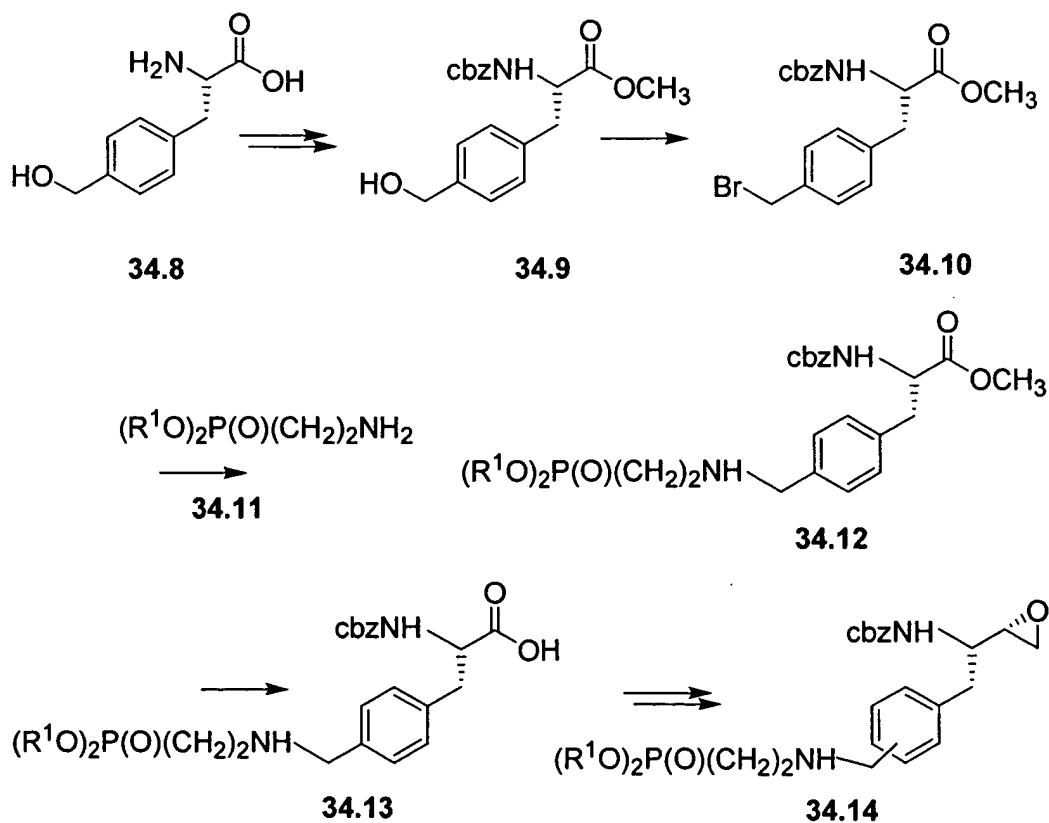


# Scheme 34

## Method



## Example



## Preparation of thiophenols 12.2 incorporating phosphonate groups

Scheme 35 illustrates the preparation of thiophenols in which a phosphonate moiety is attached directly to the aromatic ring. In this procedure, a halo-substituted thiophenol **35.1** is subjected to a suitable protection procedure. The protection of thiophenols is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 277ff. The protected compound **35.2** is then coupled, under the influence of a transition metal catalyst, with a dialkyl phosphite **30.3**, to afford the product **35.3**. The product is then deprotected to afford the free thiophenol **35.4**. Suitable protecting groups for this procedure include alkyl groups such as triphenylmethyl and the like. Palladium (0) catalysts are employed, and the reaction is conducted in an inert solvent such as benzene, toluene and the like, as described in *J. Med. Chem.*, 35, 1371, 1992. Preferably, the 3-bromothiophenol **35.5** is protected by conversion to the 9-fluorenylmethyl derivative **35.6**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 284, and the product is reacted in toluene with a dialkyl phosphite in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to yield the product **35.7**. Deprotection, for example by treatment with aqueous ammonia in the presence of an organic co-solvent, as described in *J. Chem. Soc. Chem. Comm.* 1501, 1986, then gives the thiol **35.8**.

Using the above procedures, but employing, in place of the bromo compound **35.5**, different bromo compounds **35.2**, and/or different phosphonates **30.3**, there are obtained the corresponding thiols **35.4**.

Scheme 36 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **36.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **36.3**. The latter compound is reacted with a halodialkyl phosphate **36.4**, followed by deprotection as described previously, to afford the product **36.5**.

For example, 4-bromothiophenol **36.7** is converted into the S-triphenylmethyl (trityl) derivative **36.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **36.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodiethyl phosphite **36.10** to afford the phosphonate

**36.11.** Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in *J. Org. Chem.*, 31, 1118, 1966, then affords the thiol **36.12**.

Using the above procedures, but employing, in place of the bromo compound **36.7**, different halo compounds **36.2**, and/or different halo dialkyl phosphites **36.4**, there are obtained the corresponding thiols **36.6**.

Scheme **37** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol **37.1** is subjected to free-radical bromination to afford a bromomethyl product **37.1a**. This compound is reacted with a sodium dialkyl phosphite **37.2** or a trialkyl phosphite, to give the displacement or rearrangement product **37.3**, which upon deprotection affords the thiophenols **37.4**.

For example, 2-methylthiophenol **37.5** is protected by conversion to the benzoyl derivative **37.6**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **37.7**. This material is reacted with a sodium dialkyl phosphite **37.2**, as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the product **37.8**. Alternatively, the bromomethyl compound **37.7** can be converted into the phosphonate **37.8** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **37.7** is heated with a trialkyl phosphate  $P(OR^1)_3$  at ca.  $100^{\circ}C$  to produce the phosphonate **37.8**. Deprotection of **37.8**, for example by treatment with aqueous ammonia, as described in *J. Amer. Chem. Soc.*, 85, 1337, 1963, then affords the thiol **37.9**.

Using the above procedures, but employing, in place of the bromomethyl compound **37.7**, different bromomethyl compounds **37.2**, there are obtained the corresponding thiols **37.4**.

Scheme **38** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **38.1** is reacted with a dialkyl hydroxyalkylphosphonate **38.2** under the conditions of the Mitsunobu reaction, for example as described in *Org. React.*, 1992, 42, 335, to afford the coupled product **38.3**. Deprotection then yields the O- or S-linked products **38.4**.

For example, the substrate 3-hydroxythiophenol, **38.5**, is converted into the monotrityl ether **38.6**, by reaction with one equivalent of trityl chloride, as described above. This compound

is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **38.7** in benzene, as described in *Synthesis*, 4, 327, 1998, to afford the ether compound **38.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **38.9**.

Using the above procedures, but employing, in place of the phenol **38.5**, different phenols or thiophenols **38.1**, and /or different phosphonates **38.2**, there are obtained the corresponding thiols **38.4**.

Scheme **39** illustrates the preparation of thiophenols **39.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **39.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **39.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **39.3**. Deprotection then affords the thiol **39.4**.

For example, 4-methylaminothiophenol **39.5**, is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product **39.6**. This material is then reacted with, for example, a dialkyl trifluoromethanesulfonylmethyl phosphonate **39.7**, the preparation of which is described in *Tetrahedron Lett.*, 1986, 27, 1477, to afford the displacement product **39.8**. Preferably, equimolar amounts of the phosphonate **39.7** and the amine **39.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **39.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in *J. Amer. Chem. Soc.*, 85, 1337, 1963, then affords the thiophenol **39.9**.

Using the above procedures, but employing, in place of the thioamine **39.5**, different phenols, thiophenols or amines **39.1**, and/or different phosphonates **39.2**, there are obtained the corresponding products **39.4**.

Scheme **40** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **40.2**. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol **40.1** is reacted with a dialkyl bromoalkyl phosphonate **40.2** to afford the product **40.3**. Deprotection then affords the free thiophenol **40.4**.

For example, 3-hydroxythiophenol **40.5** is converted into the S-trityl compound **40.6**, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate **40.7**, the synthesis of which is described in *Synthesis*, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product **40.8**. Deprotection, as described above, then affords the thiol **40.9**.

Using the above procedures, but employing, in place of the phenol **40.5**, different phenols, thiophenols or amines **40.1**, and/or different phosphonates **40.2**, there are obtained the corresponding products **40.4**.

Scheme **41** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **41.2** is coupled with an aromatic bromo compound **41.1**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **41.4**, or the saturated analog **41.6**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **41.7**, as described above, and this compound is reacted with diethyl 1-butenyl phosphonate **41.8**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **41.9**. Deprotection, as described above, then affords the thiol **41.10**. Optionally, the initially formed unsaturated phosphonate **41.9** can be subjected to catalytic hydrogenation, using, for example, palladium on carbon as catalyst, to yield the saturated product **41.11**, which upon deprotection affords the thiol **41.12**.

Using the above procedures, but employing, in place of the bromo compound **41.7**, different bromo compounds **41.1**, and/or different phosphonates **41.2**, there are obtained the corresponding products **41.4** and **41.6**.

Scheme **42** illustrates the preparation of an aryl-linked phosphonate ester **42.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a

phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **42.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in *J. Org. Chem.*, 49, 5237, 1984. A coupling reaction then affords the diaryl product **42.3** which is deprotected to yield the thiol **42.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in *J. Organomet. Chem.*, 1999, 581, 82, affords the boronate **42.5**. This material is reacted with diethyl 4-bromophenylphosphonate **42.6**, the preparation of which is described in *J. Chem. Soc., Perkin Trans.*, 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **42.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **42.8**.

Using the above procedures, but employing, in place of the boronate **42.5**, different boronates **42.1**, and/or different phosphonates **42.2**, there are obtained the corresponding products **42.4**.

Scheme 43 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **43.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **43.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromomethyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **43.3** is then deprotected to afford the thiol **43.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **43.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **43.5** is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, **43.6**, the preparation of which is described in *Tetrahedron*, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product **43.7** thus obtained is deprotected, as described above, to afford the thiol **43.8**.

Using the above procedures, but employing, in place of the thiophenol **43.5**, different phenols, thiophenols or amines **43.1**, and/or different phosphonates **43.2**, there are obtained the corresponding products **43.4**.

Scheme **44** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

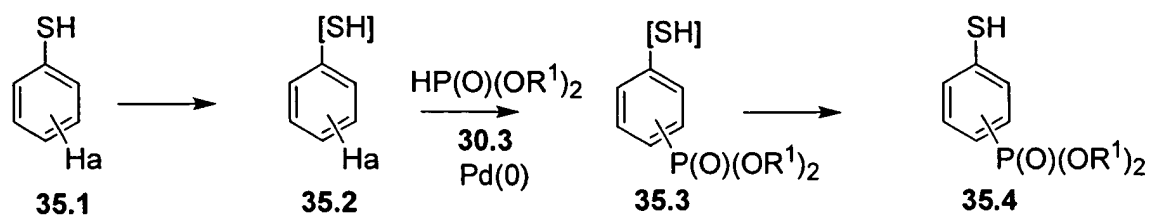
In this procedure, a suitably protected thiophenol **44.1**, for example an indoline (in which X-Y is (CH<sub>2</sub>)<sub>2</sub>), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is (CH<sub>2</sub>)<sub>3</sub>) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **44.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **44.3**. Deprotection, as described above, then affords the thiol **44.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in *J. Org. Chem.*, 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in *Synthesis*, 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in *Tetrahedron Lett.*, 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in *J. Het. Chem.*, 1991, 28, 1517, and in *J. Med. Chem.*, 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in *Sulfur Letters*, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky *et al.*, eds, Pergamon, 1995, Vol. 2, p 707.

For example, 2,3-dihydro-1H-indole-5-thiol, **44.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **44.6**, as described above, and the ester is then reacted with the triflate **44.7**, using the conditions described above for the preparation of **39.8**, (Scheme **39**, to yield the phosphonate **44.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **44.9**.

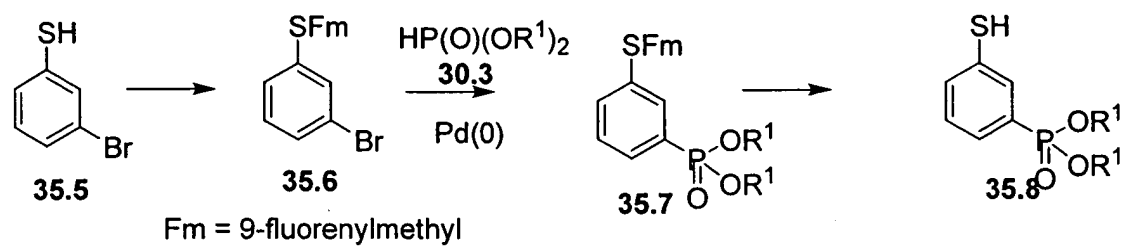
Using the above procedures, but employing, in place of the thiol **44.5**, different thiols **44.1**, and/or different triflates **44.2**, there are obtained the corresponding products **44.4**.

# Scheme 35

## Method

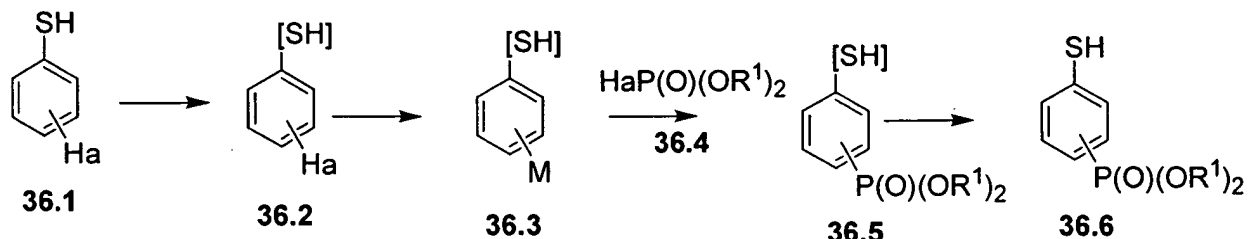


## Example

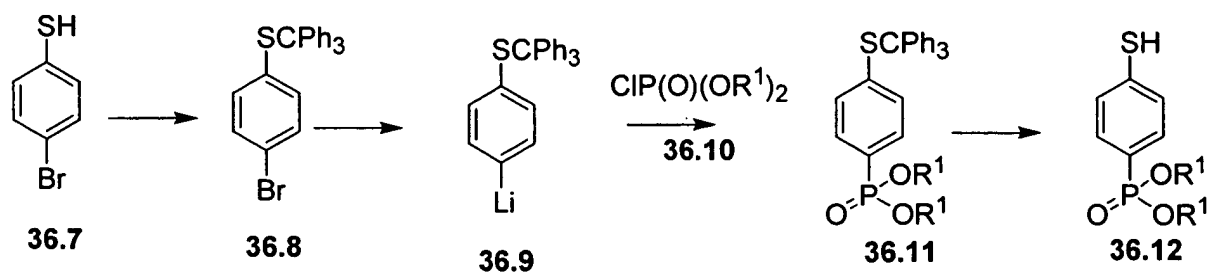


# Scheme 36

## Method

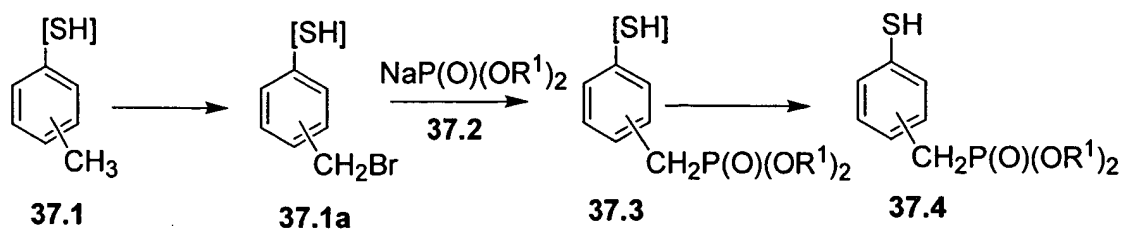


## Example

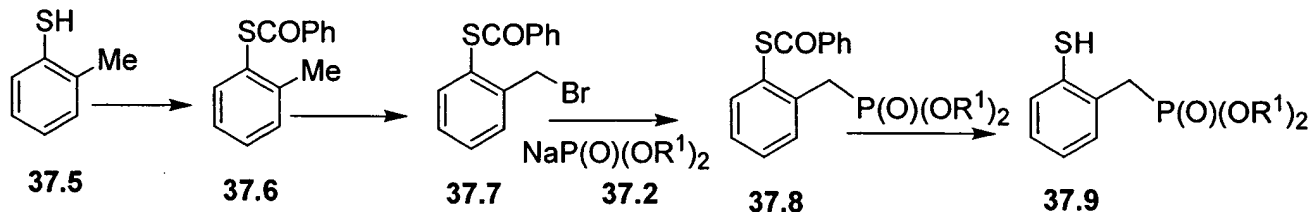


### Scheme 37

#### Method

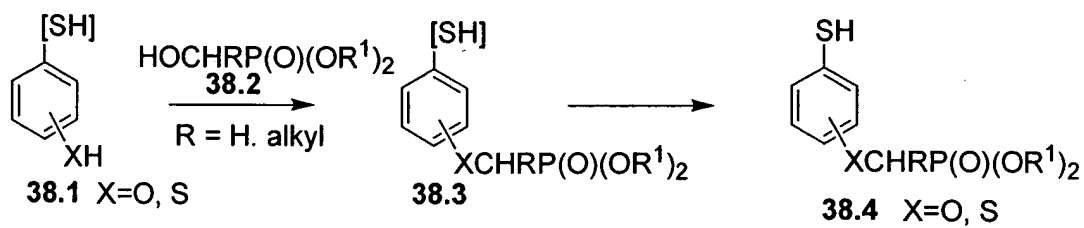


#### Example

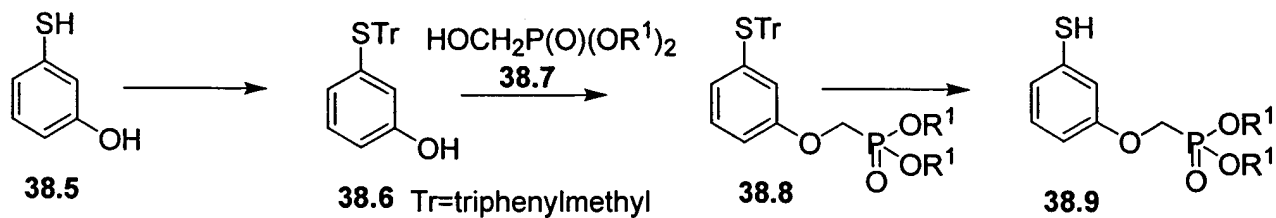


### Scheme 38

#### Method

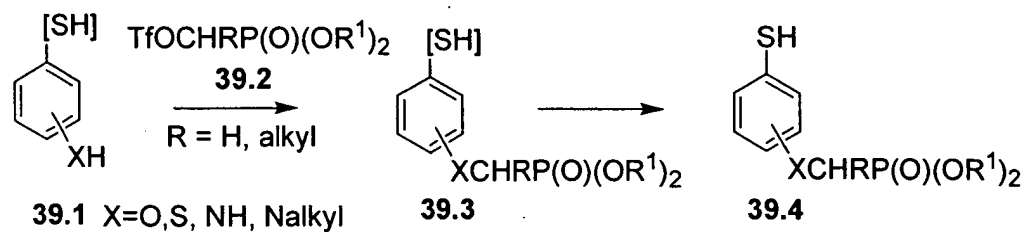


#### Example

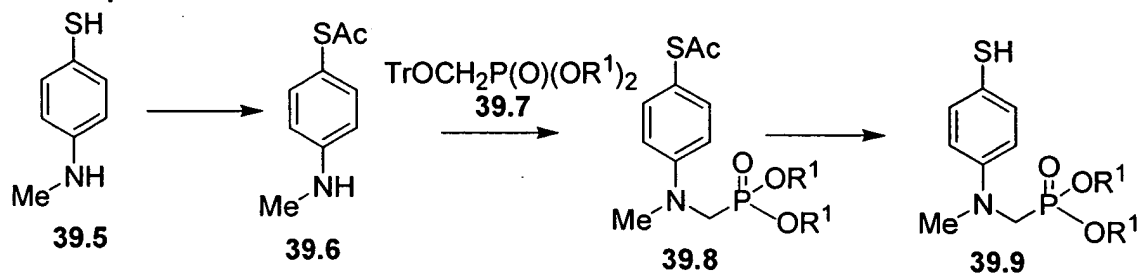


# Scheme 39

## Method

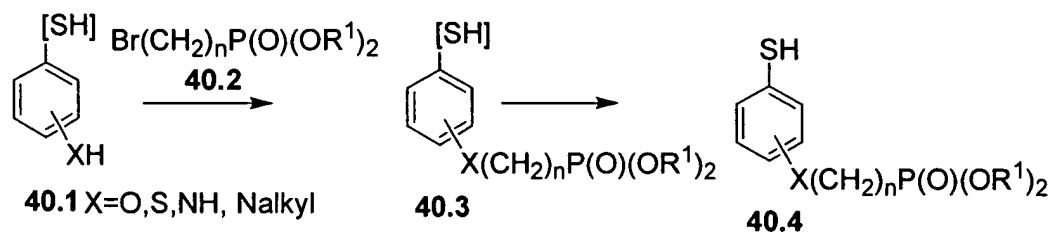


## Example

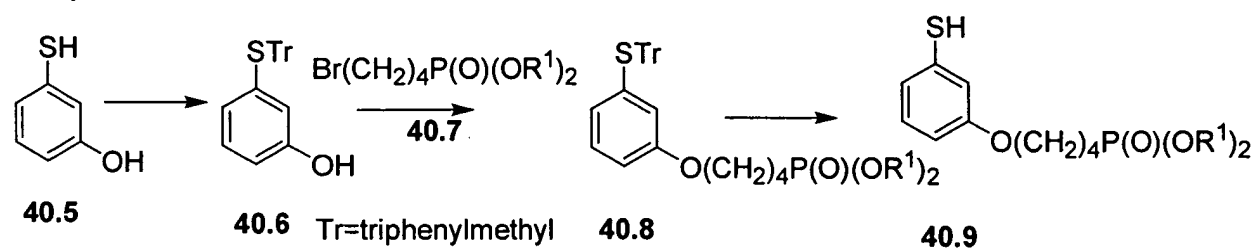


# Scheme 40

## Method

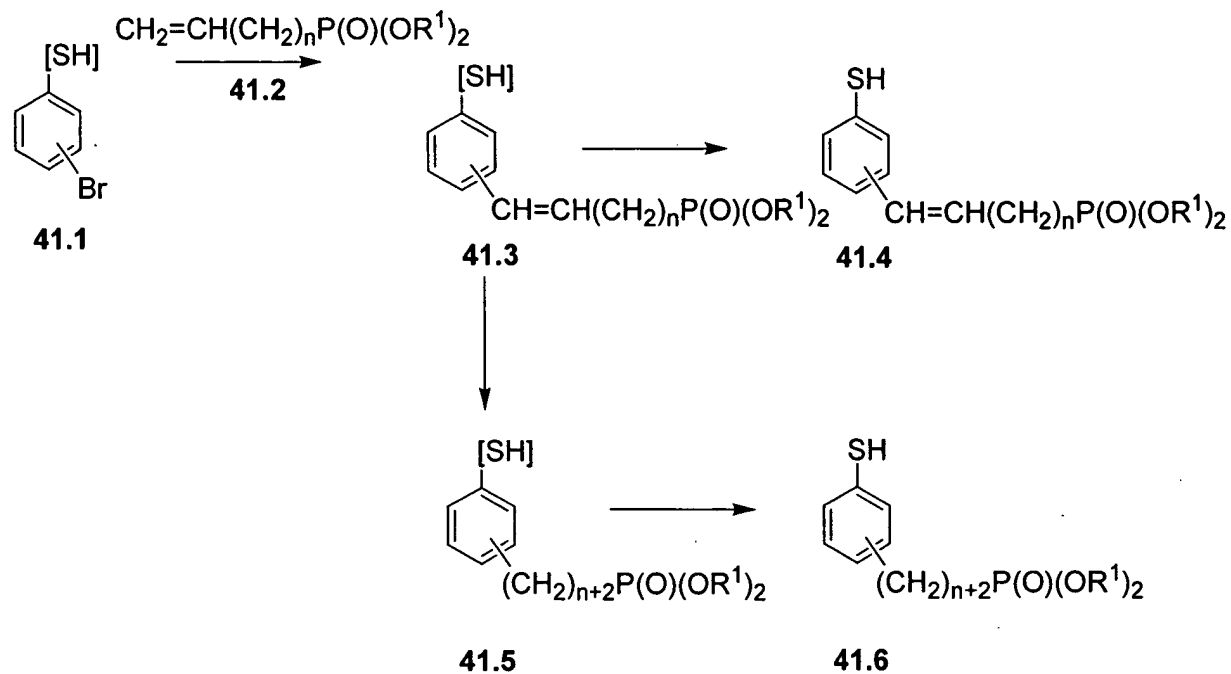


## Example

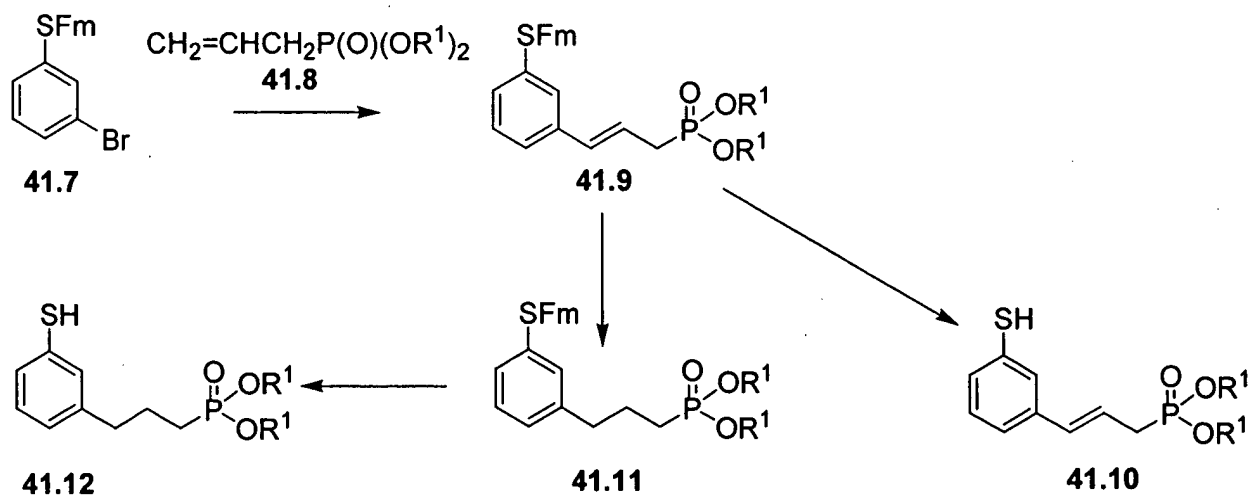


# Scheme 41

## Method

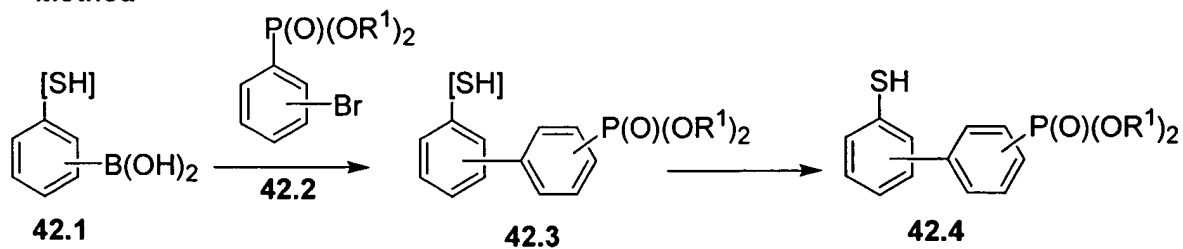


## Example

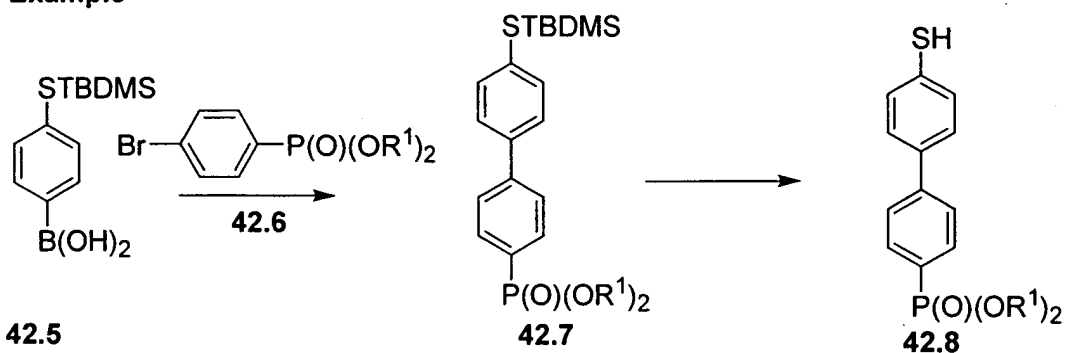


## Scheme 42

### Method



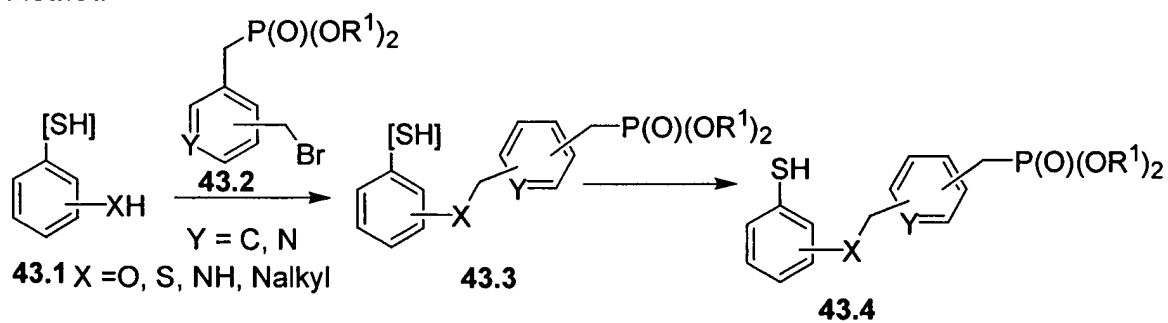
### Example



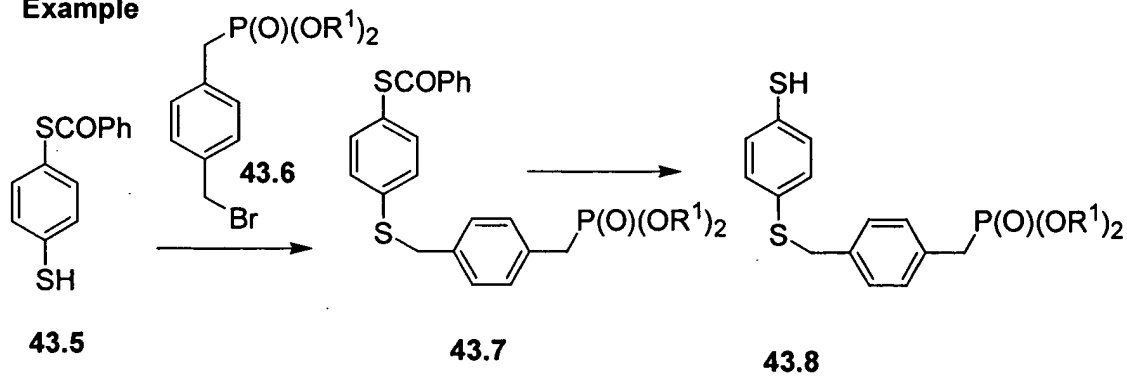
42.5

## Scheme 43

### Method



### Example



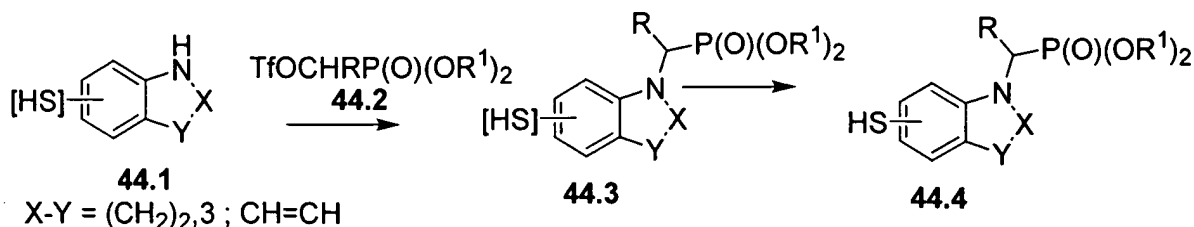
43.5

43.7

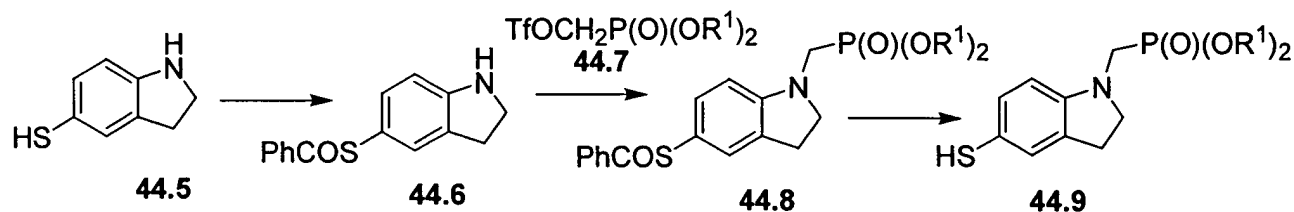
43.8

## Scheme 44

### Method



### Example



## Preparation of tert-butylamine derivatives incorporating phosphonate groups.

Scheme 45 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethyl bromide **45.1** is reacted with a trialkyl phosphite **45.2**, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate **45.3**, which is then deprotected as described previously to give **45.4**.

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide **45.6**, is heated with a trialkyl phosphite at ca 150°C to afford the product **45.7**. Deprotection, as previously described, then affords the free amine **45.8**.

Using the above procedures, but employing different trisubstituted phosphites, there are obtained the corresponding amines **45.4**.

Scheme 46 illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. An optionally protected alcohol or thiol **46.1** is reacted with a bromoalkylphosphonate **46.2**, to afford the displacement product **46.3**. Deprotection, if needed, then yields the amine **46.4**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **46.5** is reacted with a dialkyl 4-bromobutyl phosphonate **46.6**, prepared as described in *Synthesis*, 1994, 9, 909, in

dimethylformamide containing potassium carbonate and potassium iodide, at ca 60°C to afford the phosphonate **46.7**. Deprotection then affords the free amine **46.8**.

Using the above procedures, but employing different alcohols or thiols **46.1**, and/or different bromoalkylphosphonates **46.2**, there are obtained the corresponding products **46.4**.

Scheme **47** describes the preparation of carbon-linked phosphonate tert butylamine derivatives, in which the carbon chain can be unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine **47.1** is reacted, under basic conditions, with a dialkyl chlorophosphite **47.2**, as described above in the preparation of **36.5**, (Scheme **36**). The coupled product **47.3** is deprotected to afford the amine **47.4**. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **47.5** and **47.6** respectively.

For example, 2-amino-2-methylprop-1-yne **47.7**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **47.8**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°C. The resultant anion is then reacted with a dialkyl chlorophosphite **47.2** to afford the phosphonate **47.9**. Deprotection, for example by treatment with hydrazine, as described in *J. Org. Chem.*, 43, 2320, 1978, then affords the free amine **47.10**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p 566, produces the olefinic phosphonate **47.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **47.12**.

Using the above procedures, but employing different acetylenic amines **47.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **47.4**, **47.5** and **47.6**.

Scheme **48** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

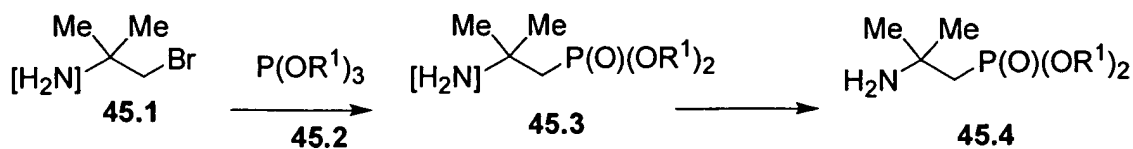
In this method, an aminoethyl-substituted cyclic amine **48.1** is reacted with a limited amount of a bromoalkyl phosphonate **48.2**, using, for example, the conditions described above for the preparation of **40.3**, (Scheme **40**) to afford the displacement product **48.3**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **48.4**, the preparation of which is described in *Chem. Pharm. Bull.*, 1994, 42, 1442, is reacted with a dialkyl 4-bromobutyl phosphonate **48.5**, prepared as described in *Synthesis*, 1994, 9, 909, to afford the displacement product **48.6**.

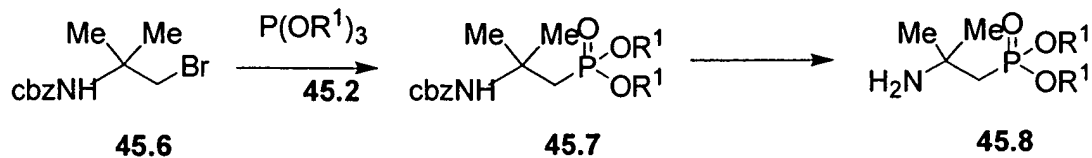
Using the above procedures, but employing different cyclic amines **48.1**, and/or different bromoalkylphosphonates **48.2**, there are obtained the corresponding products **48.3**.

# Scheme 45

## Method

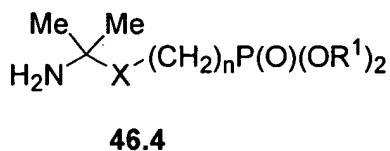
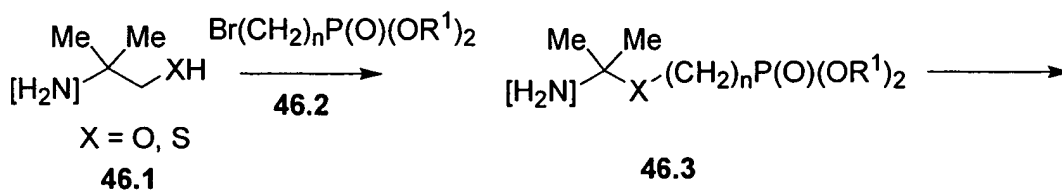


## Example

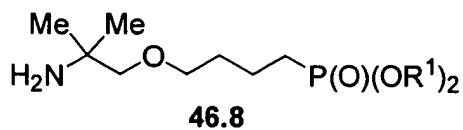
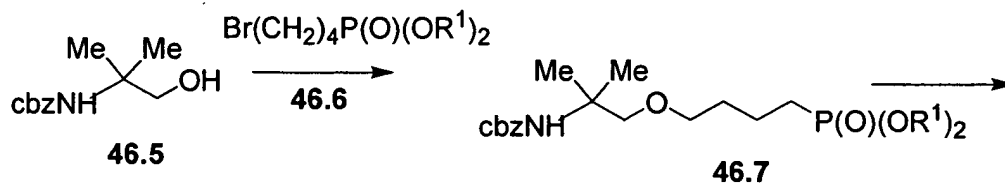


# Scheme 46

## Method



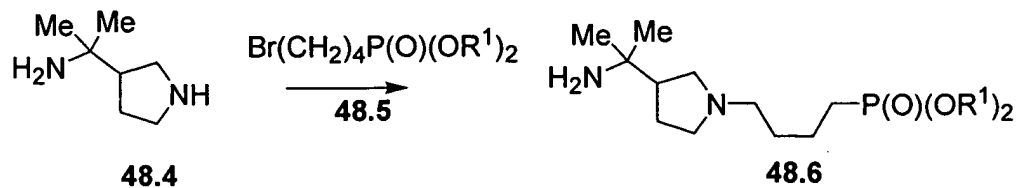
## Example



## Method



## Method



### Preparation of decahydroquinolines with phosphonate moieties at the 6-position

Scheme 48a illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the intermediate **48a.4** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **48a.1**, the preparation of which is described in *J. Med. Chem.*, 1969, 12, 1028, is converted into the protected derivative **48a.2**. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product **48a.2**, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product **48a.3**. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound **48a.3** is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline **48a.4**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **48a.4** can be obtained from 2-hydroxyphenylalanine **48a.5**, the preparation of which is described in *Can. J. Bioch.*, 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in *Chem. Rev.*, 1995, 95, 1797.

Typically, the substrate **48a.5** is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in *J. Med. Chem.*, 1986, 29, 784, to afford the tetrahydroisoquinoline product **48a.4**, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, platinum as catalyst, as described in *J. Amer. Chem. Soc.*, 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in *J. Med. Chem.*, 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline **48a.6**. The reduction can also be performed electrochemically, as described in *Trans SAEST* 1984, 19, 189.

For example, the tetrahydroisoquinoline **48a.4** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°C, to afford the decahydroisoquinoline **48a.6**.

Protection of the carboxyl and NH groups present in **48a.6** for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **48a.9**, in which R is trichloroethyl and R<sub>1</sub> is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in *J. Amer. Chem. Soc.*, 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in *J. Amer. Chem. Soc.*, 80, 5372, 1958, then affords the alcohol **48a.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **48a.10**.

The alcohol **48a.6** can be converted into the thiol **48a.13** and the amine **48a.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol **48a.6** can be converted into an activated ester such as the trifluoromethanesulfonyl ester or the methanesulfonate ester **48a.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **48a.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in *Tetrahedron Lett.*, 1992, 4099, or sodium thiophosphate, as described in *Acta Chem. Scand.*, 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **48a.13**.

For example, the mesylate **48a.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **48a.12**, in which R is COCH<sub>3</sub>. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **48a.13**.

The mesylate **48a.7** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, followed by deprotection as described previously, to afford the amine **48a.14**.

For example, the mesylate **48a.7** is reacted, as described in *Angew. Chem. Int. Ed.*, 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **48a.8**, in which  $\text{NR}^a\text{R}^b$  is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in *J. Org. Chem.*, 38, 3034, 1973, then yields the amine **48a.14**.

The application of the procedures described above for the conversion of the  $\beta$ -carbinol **48a.6** to the  $\alpha$ -thiol **48a.13** and the  $\alpha$ -amine **48a.14** can also be applied to the  $\alpha$ -carbinol **48a.10**, so as to afford the  $\beta$ -thiol and  $\beta$ -amine, **48a.11**.

Scheme 49 illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.

In this procedure, an alcohol, thiol or amine **49.1** is reacted with a bromoalkyl phosphonate **49.2**, under the conditions described above for the preparation of the phosphonate **40.3** (Scheme 40), to afford the displacement product **49.3**. Removal of the ester group, followed by conversion of the acid to the  $\text{R}^4\text{NH}$  amide and N-deprotection, as described below, (Scheme 53) then yields the amine **49.8**.

For example, the compound **49.5**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **49.6**, the preparation of which is described in *J. Amer. Chem. Soc.*, 2000, 122, 1554 to afford the displacement product **49.7**. Deprotection of the ester group, followed by conversion of the acid to the  $\text{R}^4\text{NH}$  amide and N-deprotection, as described below, (Scheme 53) then yields the amine **49.8**.

Using the above procedures, but employing, in place of the  $\alpha$ -thiol **49.5**, the alcohols, thiols or amines **48a.6**, **48a.10**, **48a.11**, **48a.13**, **48a.14**, of either  $\alpha$ - or  $\beta$ -orientation, there are obtained the corresponding products **49.4**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 50 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **48a.14** or **48a.11** are reacted with a phosphonate aldehyde **50.1**, in the presence of a reducing agent, to afford the alkylated amine **50.2**. Deprotection of the

ester group, followed by conversion of the acid to the R<sup>4</sup>NH amide and N-deprotection, as described below, (Scheme 53) then yields the amine 50.3.

For example, the protected amino compound 48a.14 is reacted with a dialkyl formylphosphonate 50.4, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in *Org. Prep. Proc. Int.*, 11, 201, 1979, to give the amine phosphonate 50.5. Deprotection of the ester group, followed by conversion of the acid to the R<sup>4</sup>NH amide and N-deprotection, as described below, (Scheme 53) then yields the amine 50.6.

Using the above procedures, but employing, instead of the  $\alpha$ -amine 48a.14, the  $\beta$  isomer, 48a.11 and/or different aldehydes 50.1, there are obtained the corresponding products 50.3, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme 51 depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate 51.2 is reacted with a mesylate 51.1, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product 51.3. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 53) then yields the amine 51.4.

For example, the protected mesylate 51.5 is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate 51.6, the preparation of which is described in *Aust. J. Chem.*, 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate 51.7. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 53) then yields the amine 51.8

Using the above procedures, but employing, instead of the phosphonate 51.6, different phosphonates 51.2, there are obtained the corresponding products 51.4.

Scheme 52 illustrates the preparation of decahydroisoquinoline phosphonates 52.4 in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 52.1 and a bromomethyl substituted phosphonate 52.2. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the

nature of the reactant **52.1**. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds **52.3**. Deprotection of the ester group, followed by conversion of the acid to the R<sup>4</sup>NH amide and N-deprotection, as described below, (Scheme 53) then yields the amine **52.4**.

For example, the protected alcohol **52.5** is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate **52.6**, the preparation of which is described above, (Scheme 43). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **52.6**, to afford the product **52.7**. Deprotection of the ester group, followed by conversion of the acid to the R<sup>4</sup>NH amide and N-deprotection, as described below, (Scheme 53) then yields the amine **52.8**.

Using the above procedures, but employing, instead of the  $\beta$ -carbinol **52.5**, different carbinols, thiols or amines **52.1**, of either  $\alpha$ - or  $\beta$ -orientation, and/or different phosphonates **52.2**, in place of the phosphonate **52.6**, there are obtained the corresponding products **52.4** in which the orientation of the side-chain is the same as that of the starting material **52.1**.

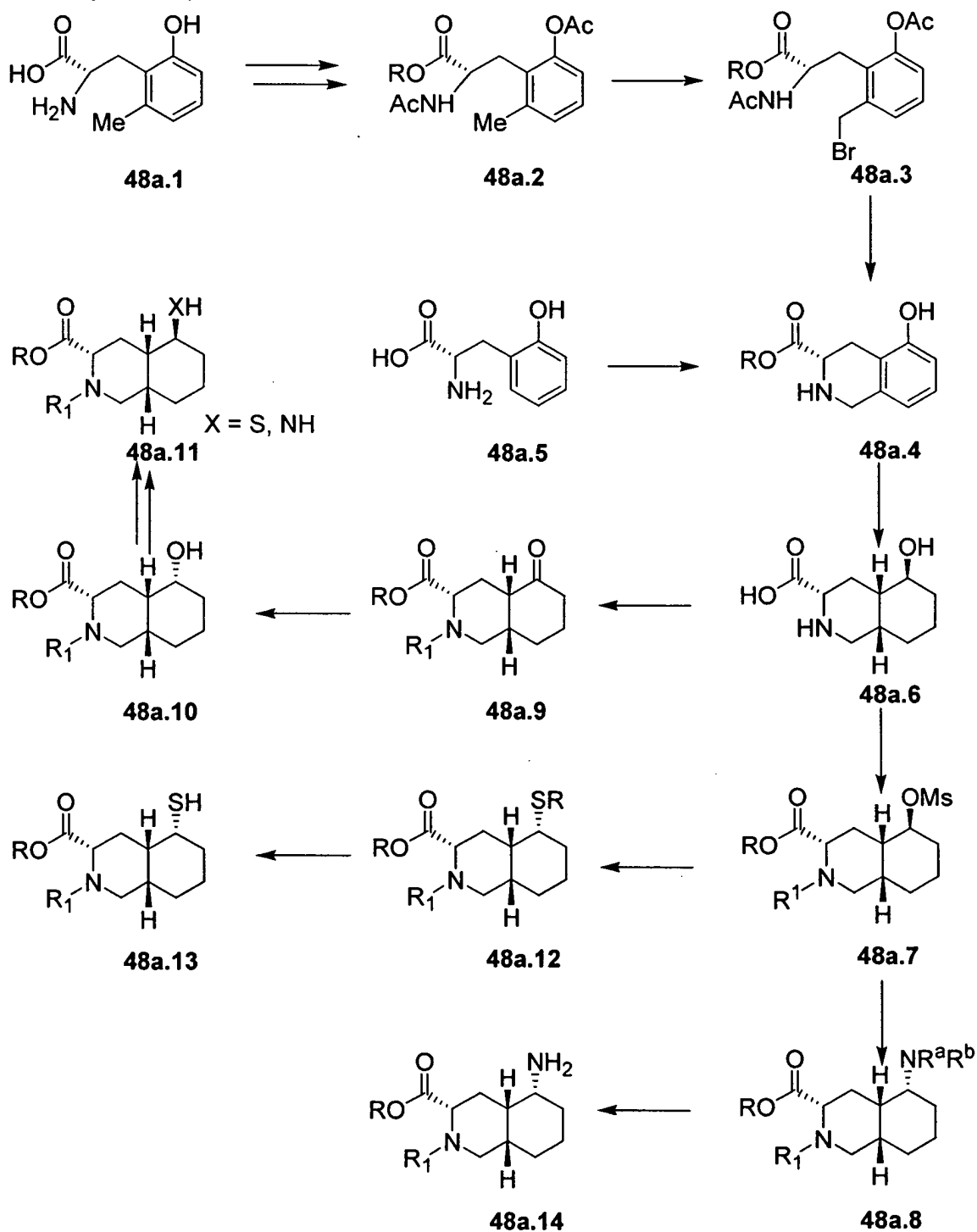
Schemes 49-52 illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme 53 illustrates the conversion of the latter group of compounds **53.1** (in which the group B is link-P(O)(OR<sup>1</sup>)<sub>2</sub> or optionally protected precursor substituents thereto, such as, for example, OH, SH, NH<sub>2</sub>) to the corresponding R<sup>4</sup>NH amides **53.5**.

As shown in Scheme 53, the ester compounds **53.1** are deprotected to form the corresponding carboxylic acids **53.2**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R<sup>2</sup>, and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in *J. Amer. Chem. Soc.*, 88, 852, 1966. Conversion of the carboxylic acid **53.2** to the R<sup>4</sup>NH amide **53.4** is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with the amine R<sup>4</sup>NH<sub>2</sub> **53.3** to

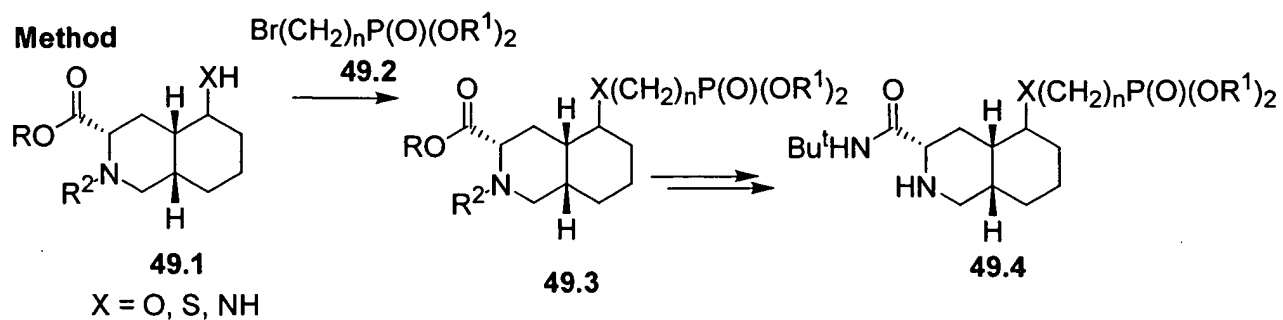
afford the amide **53.4**, using the conditions described above for the preparation of the amide **1.6**. Deprotection of the  $\text{NR}^2$  group, as described above, then affords the free amine **53.5**.

**Scheme 48a. Intermediates for the preparation of phosphonate-containing decahydroisoquinolines.**

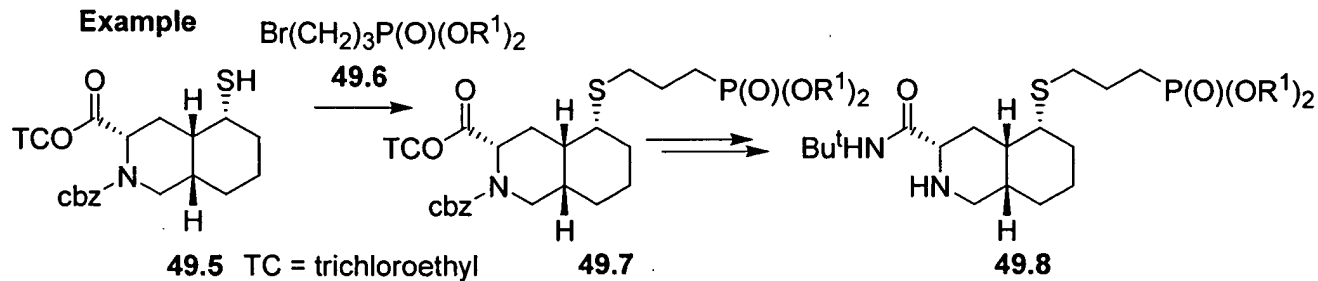


### Scheme 49

#### Method

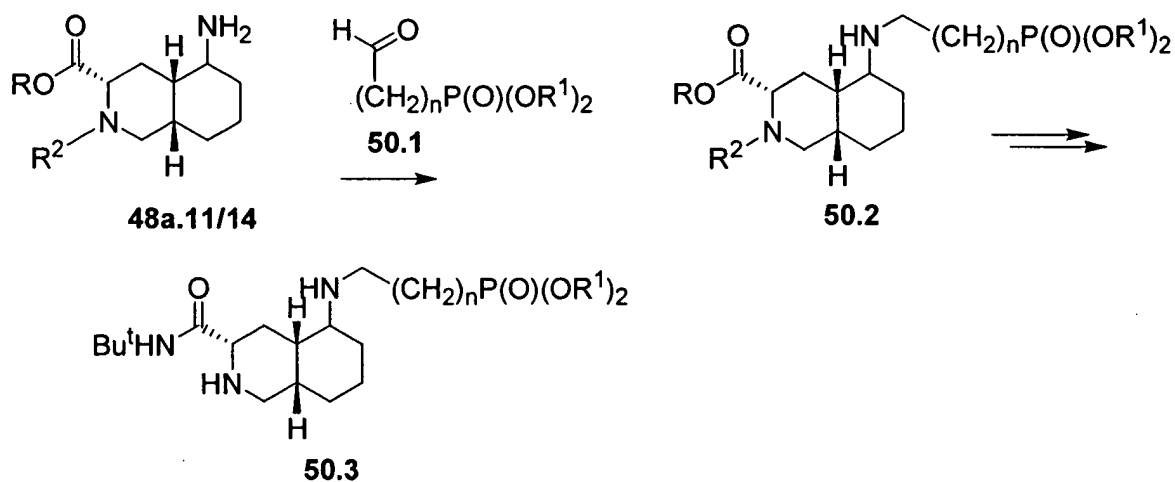


#### Example

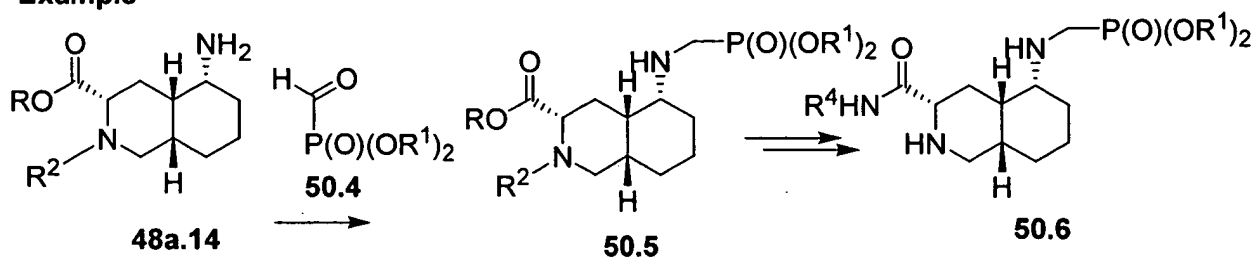


### Scheme 50

#### Method

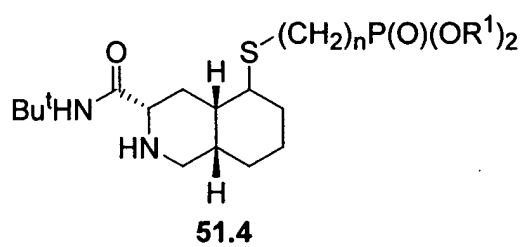
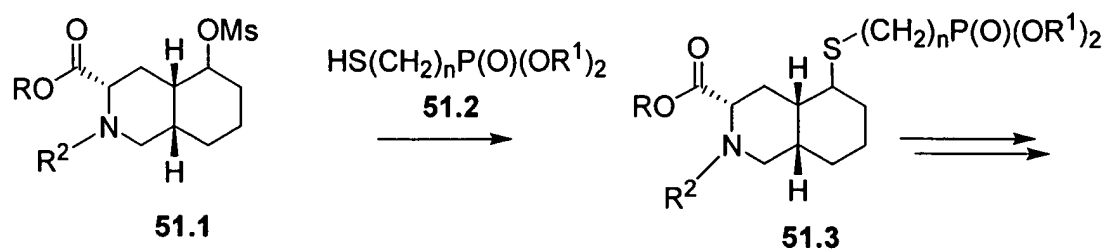


#### Example

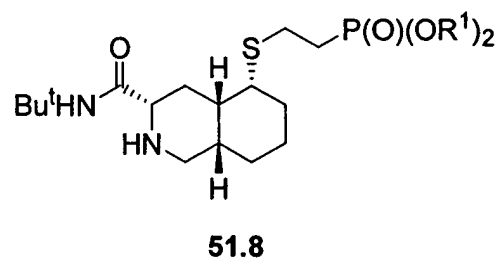
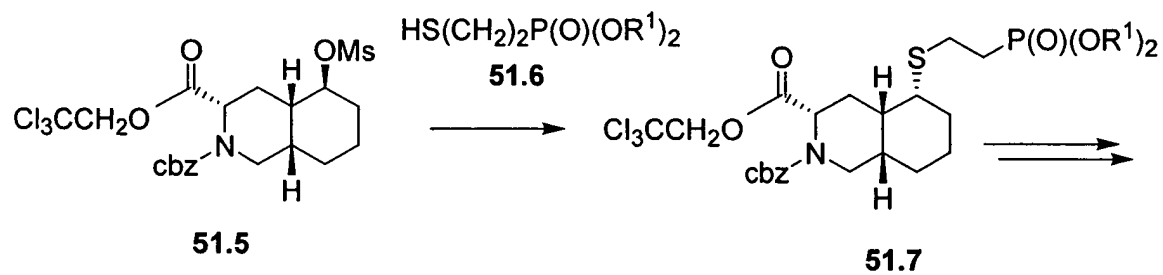


# Scheme 51

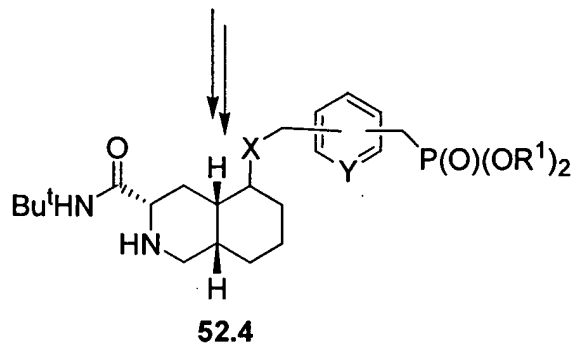
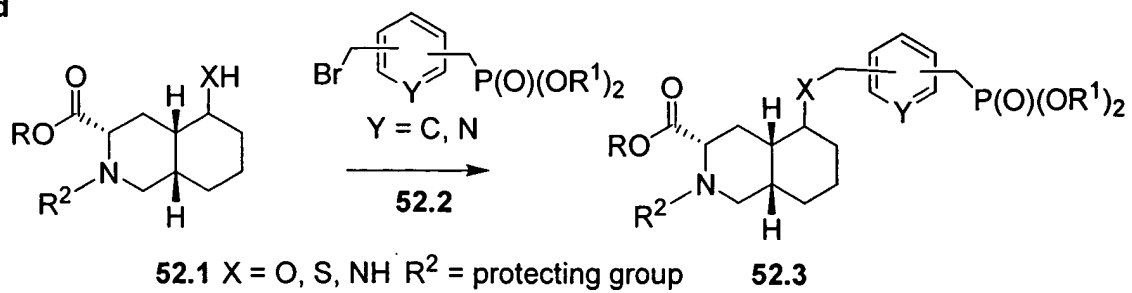
## Method



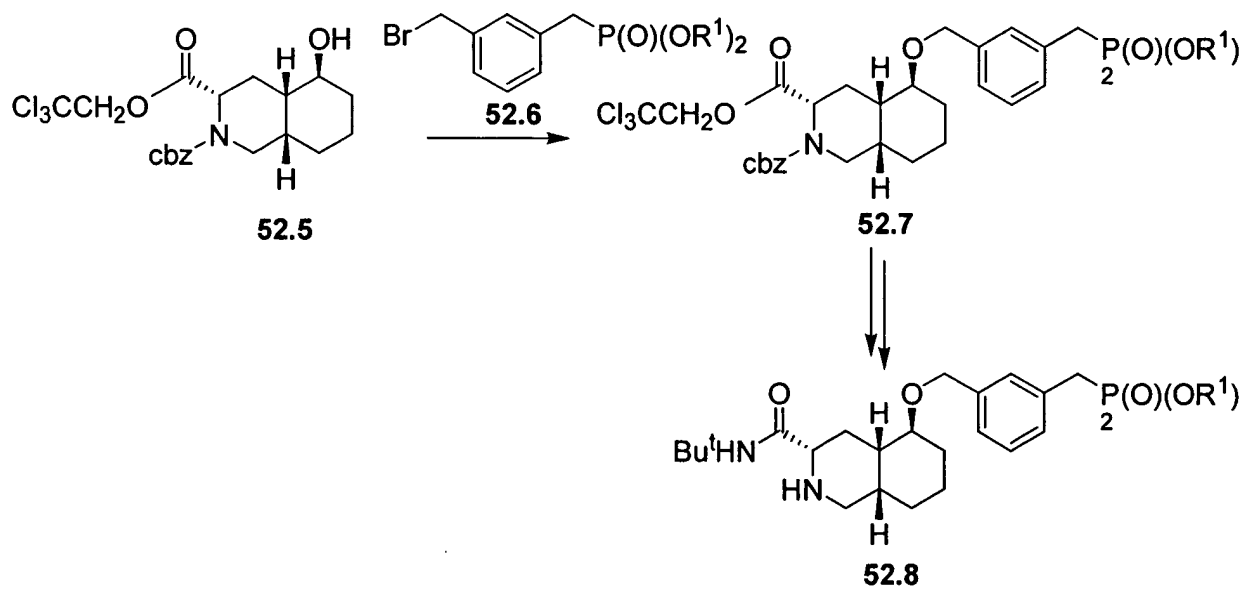
## Example



**Scheme 52**  
**Method**

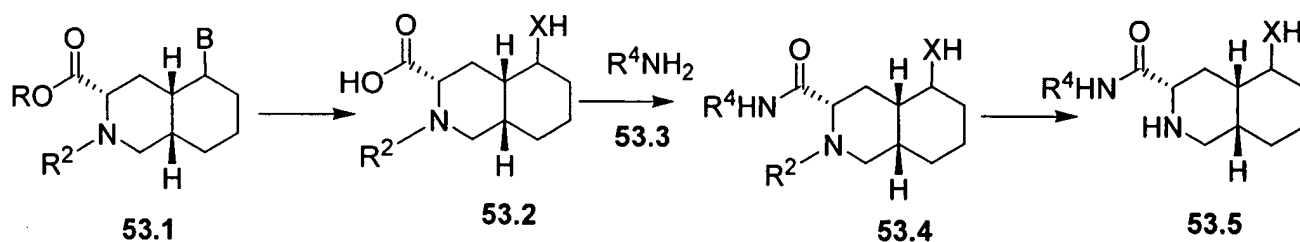


**Example**

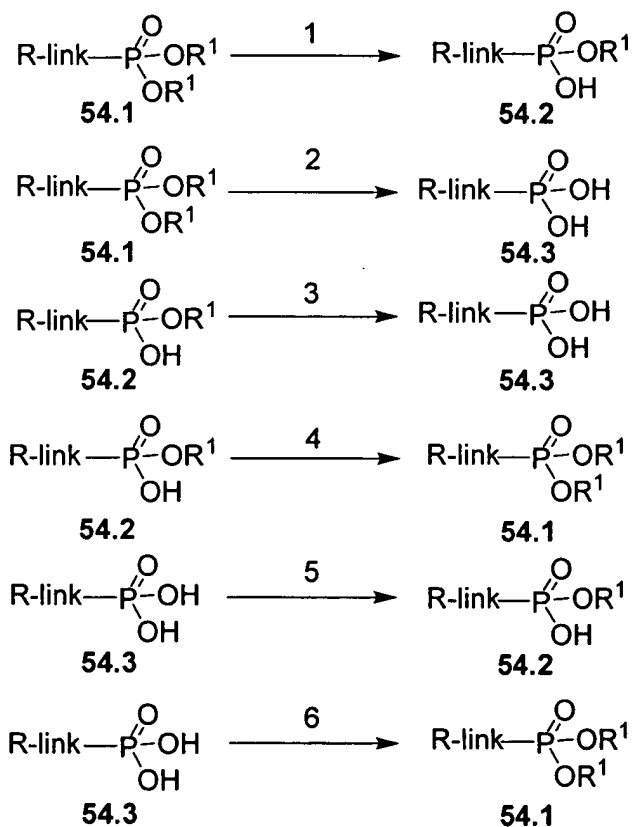


### Scheme 53

#### Method



### Scheme 54



### Interconversions of the phosphonates

#### R-link-P(O)(OR<sup>1</sup>)<sub>2</sub>, R-link-P(O)(OR<sup>1</sup>)(OH) and R-link-P(O)(OH)<sub>2</sub>

Schemes 1 - 69 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR<sup>1</sup>)<sub>2</sub>, in which the groups R<sup>1</sup>, the structures of which are defined in Chart 1, may be the same or different. The R<sup>1</sup> groups attached to a phosphonate esters 1-6, or to precursors thereto, may be changed using established chemical transformations. The interconversions

reactions of phosphonates are illustrated in Scheme 54. The group R in Scheme 54 represents the substructure to which the substituent link-P(O)(OR<sup>1</sup>)<sub>2</sub> is attached, either in the compounds 1-6 or in precursors thereto. The R<sup>1</sup> group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-6. The methods employed for a given phosphonate transformation depend on the nature of the substituent R<sup>1</sup>. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 54.1 into the corresponding phosphonate monoester 54.2 (Scheme 54, Reaction 1) can be accomplished by a number of methods. For example, the ester 54.1 in which R<sup>1</sup> is an aralkyl group such as benzyl, can be converted into the monoester compound 54.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 54.1 in which R<sup>1</sup> is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 54.2 can be effected by treatment of the ester 54.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 54.1 in which one of the groups R<sup>1</sup> is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 54.2 in which R<sup>1</sup> is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R<sup>1</sup> are alkenyl, such as allyl, can be converted into the monoester 54.2 in which R<sup>1</sup> is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.*, 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 54.1 or a phosphonate monoester 54.2 into the corresponding phosphonic acid 54.3 (Scheme 54, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 54.2 in which R<sup>1</sup> is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 54.3

by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **54.2** in which R<sup>1</sup> is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **54.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **54.1** in which R<sup>1</sup> is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **54.1** in which R<sup>1</sup> is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

The conversion of a phosphonate monoester **54.2** into a phosphonate diester **54.1** (Scheme 54, Reaction 4) in which the newly introduced R<sup>1</sup> group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **54.2** is reacted with a hydroxy compound R<sup>1</sup>OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **54.2** to the diester **54.1** can be effected by the use of the Mitsunobu reaction, as described above (Scheme 25). The substrate is reacted with the hydroxy compound R<sup>1</sup>OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **54.2** can be transformed into the phosphonate diester **54.1**, in which the introduced R<sup>1</sup> group is alkenyl or aralkyl, by reaction of the monoester with the halide R<sup>1</sup>Br, in which R<sup>1</sup> is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **54.2** is transformed into the chloro analog RP(O)(OR<sup>1</sup>)Cl by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product

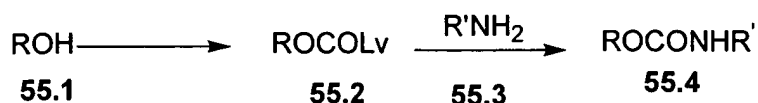
$\text{RP(O)(OR}^1\text{)Cl}$  is then reacted with the hydroxy compound  $\text{R}^1\text{OH}$ , in the presence of a base such as triethylamine, to afford the phosphonate diester **54.1**.

A phosphonic acid  $\text{R-link-P(O)(OH)}_2$  can be transformed into a phosphonate monoester  $\text{RP(O)(OR}^1\text{)(OH)}$  (Scheme 54, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester  $\text{R-link-P(O)(OR}^1\text{)}_2$  **54.1**, except that only one molar proportion of the component  $\text{R}^1\text{OH}$  or  $\text{R}^1\text{Br}$  is employed.

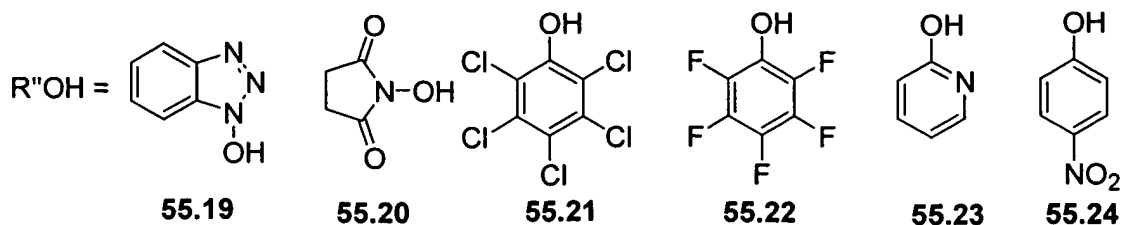
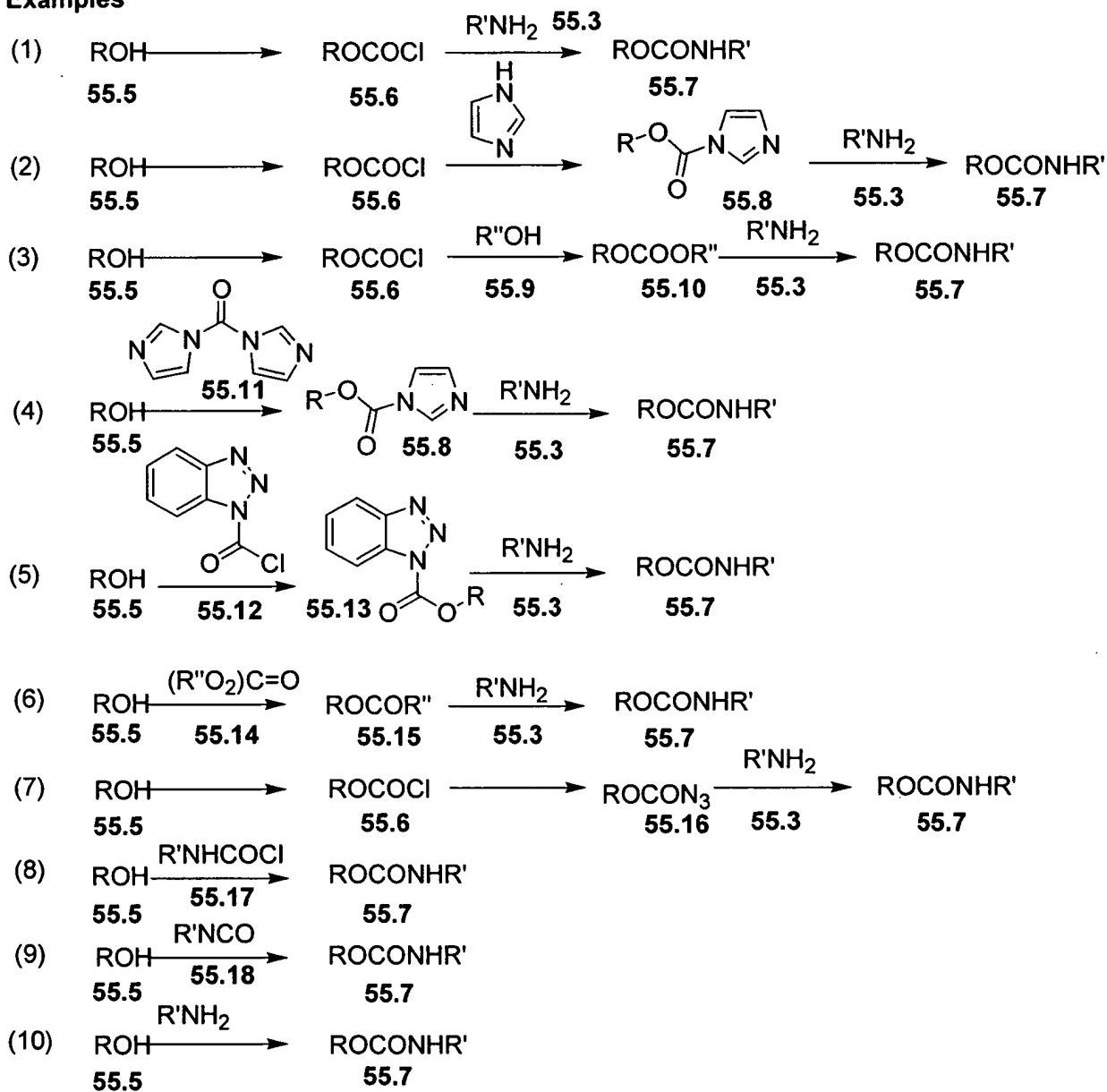
A phosphonic acid  $\text{R-link-P(O)(OH)}_2$  **54.3** can be transformed into a phosphonate diester  $\text{R-link-P(O)(OR}^1\text{)}_2$  **54.1** (Scheme 54, Reaction 6) by a coupling reaction with the hydroxy compound  $\text{R}^1\text{OH}$ , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **54.3** can be transformed into phosphonic esters **54.1** in which  $\text{R}^1$  is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca  $70^\circ\text{C}$ . Alternatively, phosphonic acids **54.3** can be transformed into phosphonic esters **54.1** in which  $\text{R}^1$  is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide  $\text{R}^1\text{Br}$  in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **54.1**.

# Scheme 55

## General reaction



## Examples



### Preparation of the phosphonate esters 1-6 incorporating carbamate moieties

The phosphonate esters 1-6 in which the  $R^6CO$  group is formally derived from the carboxylic acid synthons **C39** - **C49** as shown in Chart 2c, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme 55 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 55, in the general reaction generating carbamates, a carbinol **55.1** is converted into the activated derivative **55.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **55.2** is then reacted with an amine **55.3**, to afford the carbamate product **55.4**. Examples 1 – 7 in Scheme 55 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 55, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **55.5**. In this procedure, the carbinol **55.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in *Org. Syn. Coll.* Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in *Org. Syn. Coll.* Vol. 6, 715, 1988, to afford the chloroformate **55.6**. The latter compound is then reacted with the amine component **55.3**, in the presence of an organic or inorganic base, to afford the carbamate **55.7**. For example, the chloroformyl compound **55.6** is reacted with the amine **55.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in *Org. Syn. Coll.* Vol. 3, 167, 1965, to yield the carbamate **55.7**. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 55, Example 2 depicts the reaction of the chloroformate compound **55.6** with imidazole, **55.7**, to produce the imidazolide **55.8**. The imidazolide product is then reacted with the amine **55.3** to yield the carbamate **55.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in *J. Med. Chem.*, 1989, 32, 357.

Scheme 55 Example 3, depicts the reaction of the chloroformate **55.6** with an activated hydroxyl compound  $R''OH$ , to yield the mixed carbonate ester **55.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component  $R''OH$  is selected from the group of compounds **55.19** - **55.24** shown in Scheme 55, and similar compounds. For example, if the component  $R''OH$  is hydroxybenztriazole **55.19**, N-hydroxysuccinimide **55.20**, or pentachlorophenol, **55.21**, the mixed carbonate **55.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in *Can. J. Chem.*, 1982, 60, 976. A similar reaction in which the component  $R''OH$  is pentafluorophenol **55.22** or 2-hydroxypyridine **55.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in *Synthesis*, 1986, 303, and *Chem. Ber.* 118, 468, 1985.

Scheme 55 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **55.8** is employed. In this procedure, a carbinol **55.5** is reacted with an equimolar amount of carbonyl diimidazole **55.11** to prepare the intermediate **55.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **55.8** is then reacted with an equimolar amount of the amine  $R'NH_2$  to afford the carbamate **55.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in *Tetrahedron Lett.*, 42, 2001, 5227, to afford the carbamate **55.7**.

Scheme 55, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **55.13**. In this procedure, a carbinol  $ROH$  is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **55.12**, to afford the alkoxycarbonyl product **55.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in *Synthesis*, 1977, 704. This product is then reacted with the amine  $R'NH_2$  to afford the carbamate **55.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in *Synthesis*, 1977, 704.

Scheme 55, Example 6 illustrates the preparation of carbamates in which a carbonate  $(R''O)_2CO$ , **55.14**, is reacted with a carbinol **55.5** to afford the intermediate alkyloxycarbonyl intermediate **55.15**. The latter reagent is then reacted with the amine  $R'NH_2$  to afford the

carbamate **55.7**. The procedure in which the reagent **55.15** is derived from hydroxybenztriazole **55.19** is described in *Synthesis*, 1993, 908; the procedure in which the reagent **55.15** is derived from N-hydroxysuccinimide **55.20** is described in *Tetrahedron Lett.*, 1992, 2781; the procedure in which the reagent **55.15** is derived from 2-hydroxypyridine **55.23** is described in *Tetrahedron Lett.*, 1991, 4251; the procedure in which the reagent **55.15** is derived from 4-nitrophenol **55.24** is described in *Synthesis* 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **55.14** is conducted in an inert organic solvent at ambient temperature.

Scheme 55, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides **55.16**. In this procedure, an alkyl chloroformate **55.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **55.16**. The latter compound is then reacted with an equimolar amount of the amine  $R'NH_2$  to afford the carbamate **55.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in *Synthesis*, 1982, 404.

Scheme 55, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in *Synthetic Organic Chemistry*, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **55.7**.

Scheme 55, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **55.18**. In this procedure, which is described in *Synthetic Organic Chemistry*, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **55.7**.

Scheme 55, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine  $R'NH_2$ . In this procedure, which is described in *Chem. Lett.* 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **55.7**.

### **Preparation of phosphonate intermediates 5 and 6 with phosphonate moieties incorporated into the group $R^6COOH$ and $R^2NHCH(R^3)CONHR^4$**

The chemical transformations described in Schemes 1 - 55 illustrate the preparation of compounds 1-4 in which the phosphonate ester moiety is attached to the quinoline-2-carboxylate substructure, (Schemes 1-8), the phenylalanine or thiophenol moiety (Schemes 9-13), the tert-butylamine moiety (Schemes 14-18) and the decahydroisoquinoline moiety (Schemes 19 - 22).

The various chemical methods employed herein (Schemes 25 - 69) for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds  $R^6COOH$ , as defined in Charts 3a, 3b and 3c, and into the compounds  $R^2NHCH(R^3)CONHR^4$  as defined in Chart 2. For example, Schemes 56 - 61 illustrate the preparation of phosphonate-containing analogs of the phenoxyacetic acid C8 (Chart 3a), Schemes 62 - 65 illustrate the preparation of phosphonate-containing analogs of the carboxylic acid C4, Schemes 66 - 69 illustrate the preparation of phosphonate-containing analogs of the amine A12 (Chart 2), and Schemes 70-75 illustrate the preparation of phosphonate-containing analogs of the carboxylic acid C38. The resultant phosphonate-containing analogs  $R^{6a}COOH$  and  $R^{2a}NHCH(R^{3a})CONHR^4$  can then, using the procedures described above, be employed in the preparation of the compounds 5 and 6. The procedures required for the introduction of the phosphonate-containing analogs  $R^{6a}COOH$  and  $R^{2a}NHCH(R^{3a})CONHR^4$  are the same as those described above for the introduction of the  $R^6CO$  and  $R^2NHCH(R^3)CONHR^4$  moieties.

### **Preparation of dimethylphenoxyacetic acids incorporating phosphonate moieties**

Scheme 56 illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol 56.1, in which the substituent B is a precursor to the group  $link-P(O)(OR^1)_2$ , and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound 56.2. Methods for the conversion of the substituent B into the group  $link-P(O)(OR^1)_2$  are described in Schemes 25 - 69.

The protected phenolic hydroxyl group present in the phosphonate-containing product **56.2** is then deprotected, using methods described below, to afford the phenol **56.3**.

The phenolic product **56.3** is then transformed into the corresponding phenoxyacetic acid **56.4**, in a two step procedure. In the first step, the phenol **56.3** is reacted with an ester of bromoacetic acid **56.5**, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **56.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in U.S. Patent 5,914,332, to afford the ester **56.6**.

The thus-obtained ester **56.6** is then hydrolyzed to afford the carboxylic acid **56.4**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product **56.6** which R is ethyl is hydrolyzed to the carboxylic acid **56.4** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in U.S. Patent 5,914,332.

Alternatively, an appropriately substituted 2,6-dimethylphenol **56.7**, in which the substituent B is a precursor to the group  $\text{link-P(O)(OR}^1\text{)}_2$ , is transformed into the corresponding phenoxyacetic ester **56.8**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **56.3** into the ester **56.6**.

The phenolic ester **56.8** is then converted, by transformation of the group B into the group  $\text{link-P(O)(OR}^1\text{)}_2$  followed by ester hydrolysis, into the carboxylic acid **56.4**. The group B which is present in the ester **56.4** may be transformed into the group  $\text{link-P(O)(OR}^1\text{)}_2$  either

before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes 56 - 61 illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids 56.8, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme 57 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds 57.4 are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde 57.1 and an aminoalkyl phosphonate ester 57.2. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component 57.2 and the aldehyde component 57.1 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 57.3. The amination product 57.3 is then converted into the phenoxyacetic acid compound 57.4, using the alkylation and ester hydrolysis procedures described above, (Scheme 56)

For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde 57.5 (Aldrich) and a dialkyl aminoethyl phosphonate 57.6, the preparation of which is described in *J. Org. Chem.*, 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in *J. Amer. Chem. Soc.*, 91, 3996, 1969, to afford the amine product 57.3. The product is then converted into the acetic acid 57.8, as described above.

Using the above procedures, but employing, in place of the aldehyde 57.5, different aldehydes 57.1, and/or different aminoalkyl phosphonates 57.2, the corresponding products 57.4 are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described above (Scheme 54)

Scheme 58 depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this

procedure, an optionally protected bromo-substituted 2,6-dimethylphenol **58.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **58.2**. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **58.3** is converted, using the procedures described above, (Scheme 56) into the corresponding phenoxyacetic acid **58.4**. Alternatively, the olefinic product **58.3** is reduced to afford the saturated 2,6-dimethylphenol derivative **58.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product **58.5** is converted, as described above, (Scheme 56) into the corresponding phenoxyacetic acid **58.6**.

For example, 3-bromo-2,6-dimethylphenol **58.7**, prepared as described in *Can. J. Chem.*, 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether **58.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **58.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **58.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°C, to produce the coupled product **58.10**. The silyl group is removed, for example by the treatment of the ether **58.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972, to afford the phenol **58.11**. This compound is converted, employing the procedures described above, (Scheme 56) into the corresponding phenoxyacetic acid **58.12**. Alternatively, the unsaturated compound **58.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **58.13**. This compound is converted, employing the procedures described above, (Scheme 56) into the corresponding phenoxyacetic acid **58.14**.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol **58.7**, different bromophenols **58.1**, and/or different dialkyl alkenyl phosphonates **58.2**, the corresponding products **58.4** and **58.6** are obtained.

Scheme **59** illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids **59.1** in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol **59.2** is converted, using the procedures illustrated in Scheme **56**, into the corresponding 2,6-dimethylphenoxyacetic ester **59.3**. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone **59.4**, in which *n* is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of **58.3** (Scheme **58**). The product **59.5** is then reduced catalytically, as described above for the reduction of **58.3**, (Scheme **58**), to afford the substituted cycloalkanone **59.6**. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoethylphosphonate **59.7** and sodium triacetoxyborohydride, as described in *J. Org. Chem.*, 61, 3849, 1996, to yield the amine phosphonate **59.8**. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine **57.3** (Scheme **57**). The resultant ester **59.8** is then hydrolyzed, as described above, to afford the phenoxyacetic acid **59.1**.

For example, 4-bromo-2,6-dimethylphenol **59.9** (Aldrich) is converted, as described above, into the phenoxy ester **59.10**. The latter compound is then coupled, in dimethylformamide solution at ca. 60°C, with cyclohexenone **59.11**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone **59.12**. The enone is then reduced to the saturated ketone **59.13**, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate **59.14**, prepared as described in *J. Org. Chem.*, 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine **59.15**. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid **59.16**.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol **59.9**, different bromo-substituted 2,6-dimethylphenols **59.2**, and/or different cycloalkenones

**59.4**, and/or different dialkyl aminoalkylphosphonates **59.7**, the corresponding products **59.1** are obtained.

Scheme **60** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol **60.1** is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **60.2**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°C. The product of the alkylation reaction, **60.3** is then converted, as described above (Scheme **56**) into the phenoxyacetic acid **60.4**.

For example, 2,6-dimethyl-4-mercaptophenol **60.5**, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60°C with an equimolar amount of a dialkyl bromobutyl phosphonate **60.6**, the preparation of which is described in *Synthesis*, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product **60.7**. This compound is converted, employing the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **60.8**.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol **60.5**, different hydroxy, thio or aminophenols **60.1**, and/or different dialkyl bromoalkyl phosphonates **60.2**, the corresponding products **60.4** are obtained.

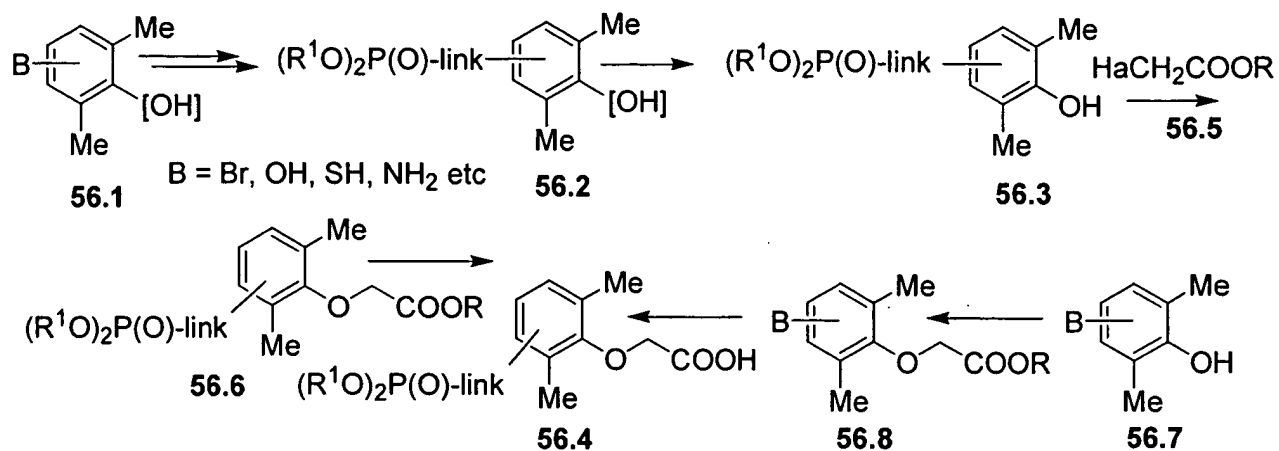
Scheme **61** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2,6-dimethylphenol **61.1** is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound **61.2**. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford the ether, thioether or amino product **61.3**. The product **61.3** is then converted, using the procedures described above, (Scheme **56**) into the phenoxyacetic ester **61.4**. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite **61.5** at ca. 100°C to afford the phosphonate ester **61.6**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in

Handb. Organophosphorus Chem., 1992, 115. The resultant product **61.6** is then converted into the acetic acid **61.7** by hydrolysis of the ester moiety, using the procedures described above, (Scheme 56).

For example, 4-hydroxy-2,6-dimethylphenol **61.8** (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in *Eur. J. Inorg. Chem.*, 1998, 2, 163, to afford the ether **61.10**. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The product **61.10** is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme 56) to afford the phenoxyacetic ester **61.11**. This product is heated at 100°C for 3 hours with three molar equivalents of triethyl phosphite **61.12**, to afford the phosphonate ester **61.13**. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid **61.14**.

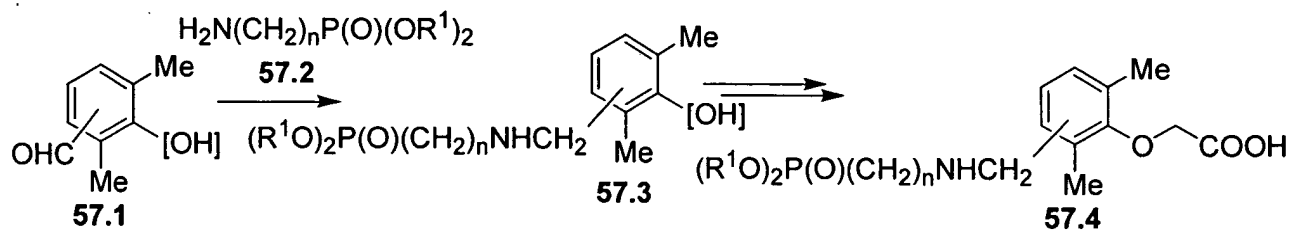
Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine **61.9**, different bis(halomethyl) aromatic or heteroaromatic compounds **61.2**, and/or different hydroxy, mercapto or amino-substituted 2,6-dimethylphenols **61.1** and/or different trialkyl phosphites **61.5**, the corresponding products **61.7** are obtained.

### Scheme 56

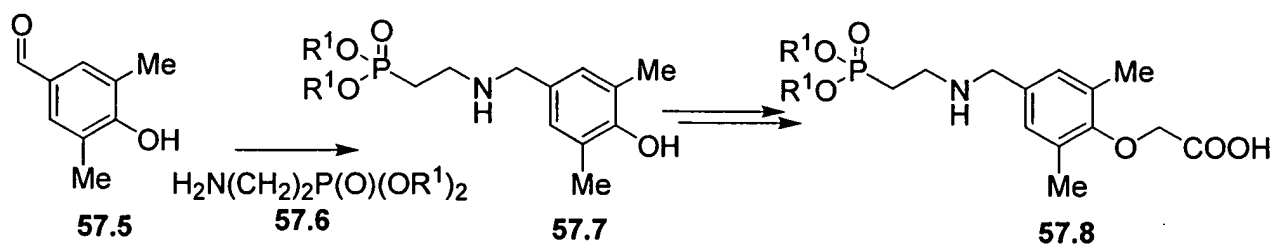


### Scheme 57

#### Method

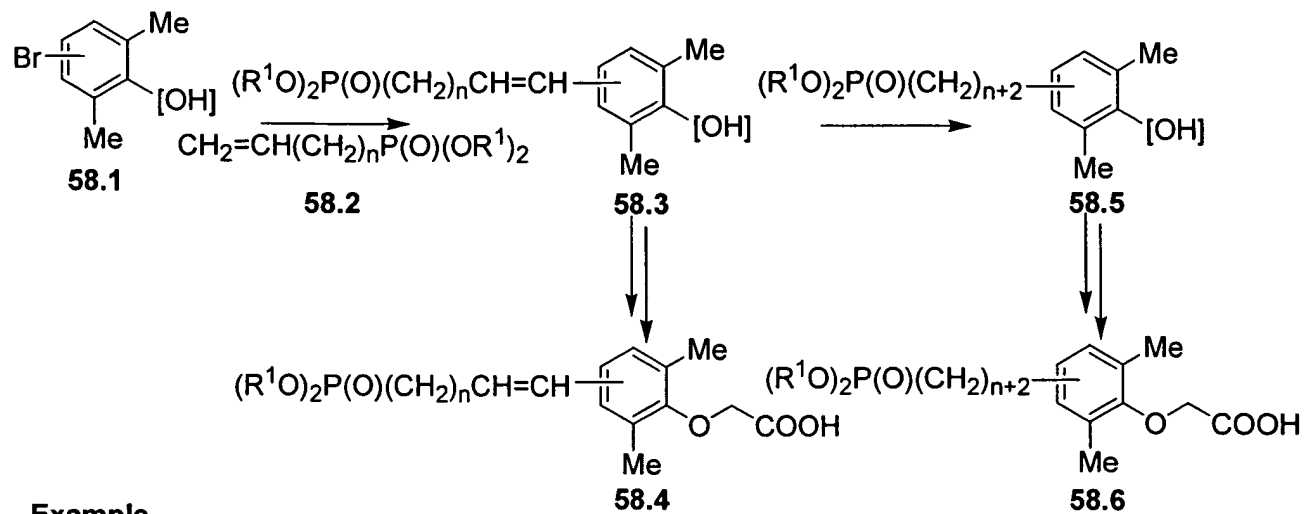


#### Example

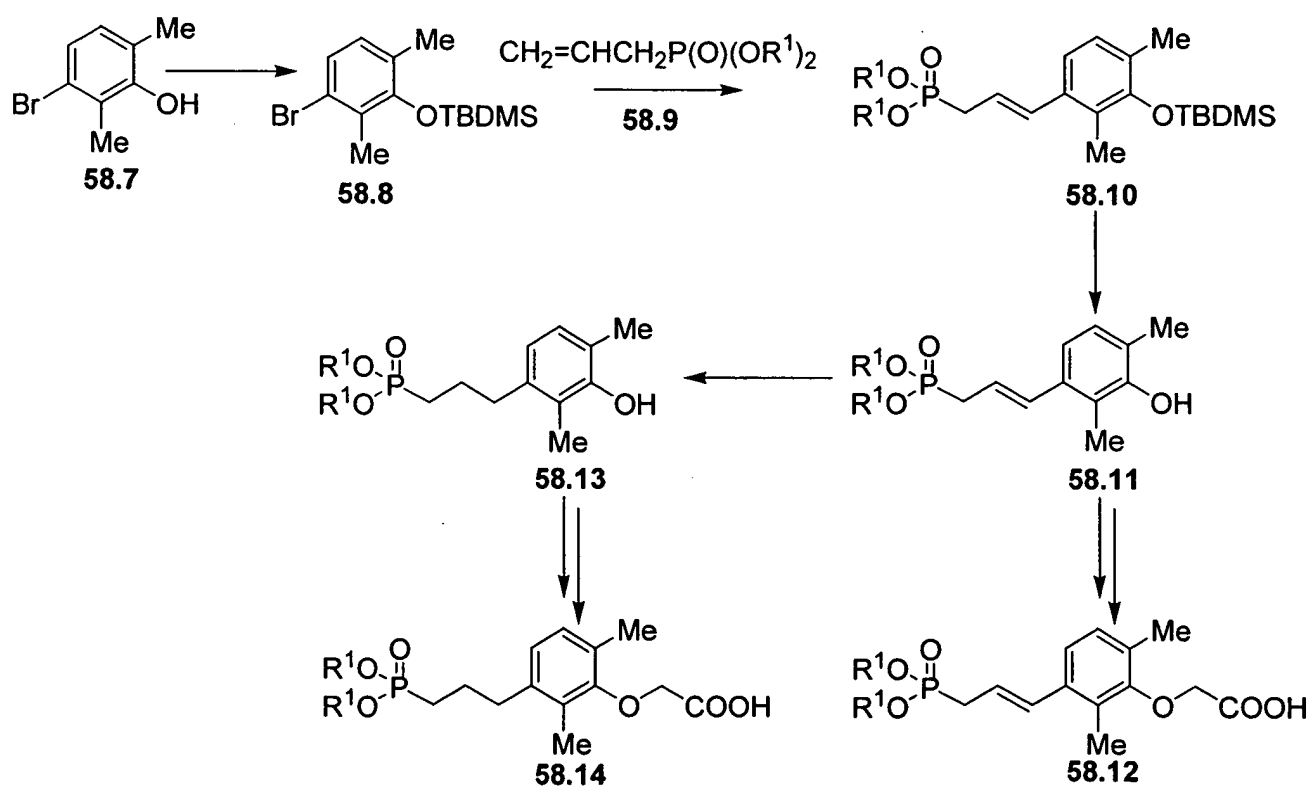


# Scheme 58

## Method

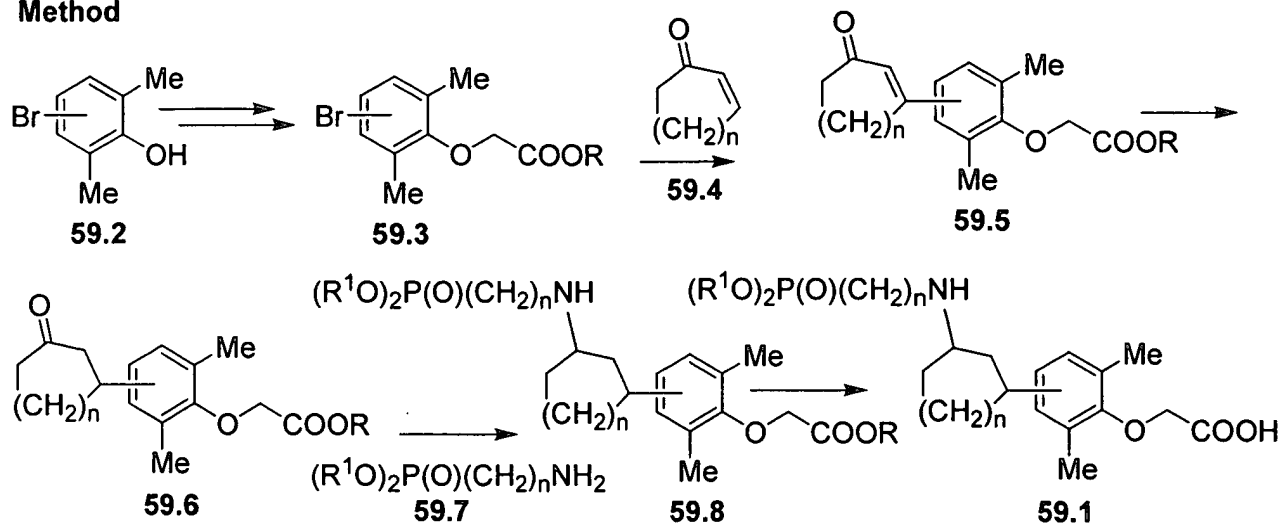


## Example

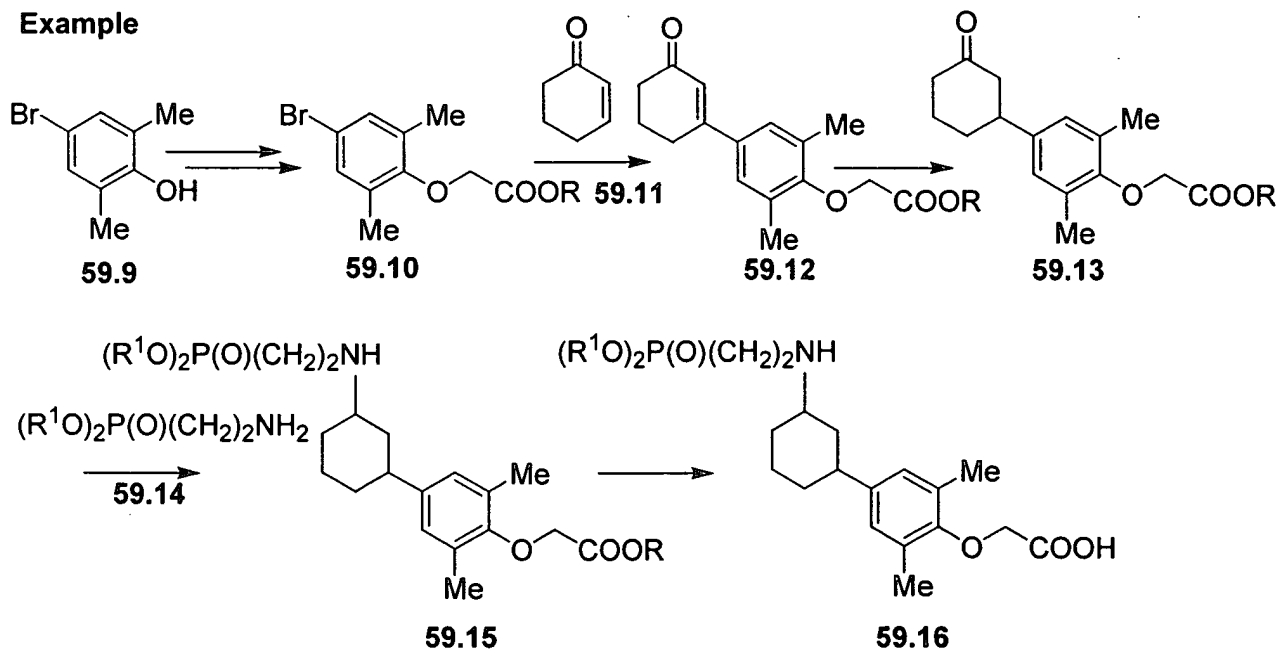


# Scheme 59

## Method

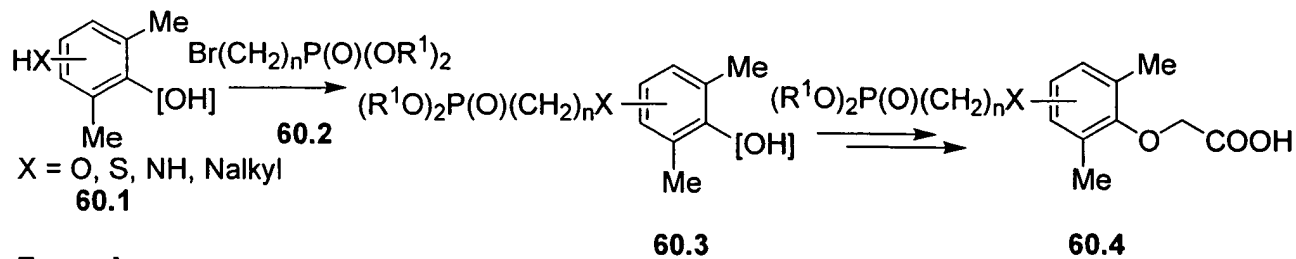


## Example

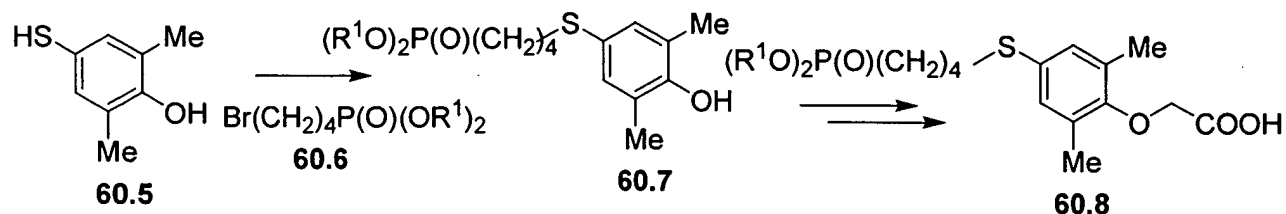


## Scheme 60

### Method

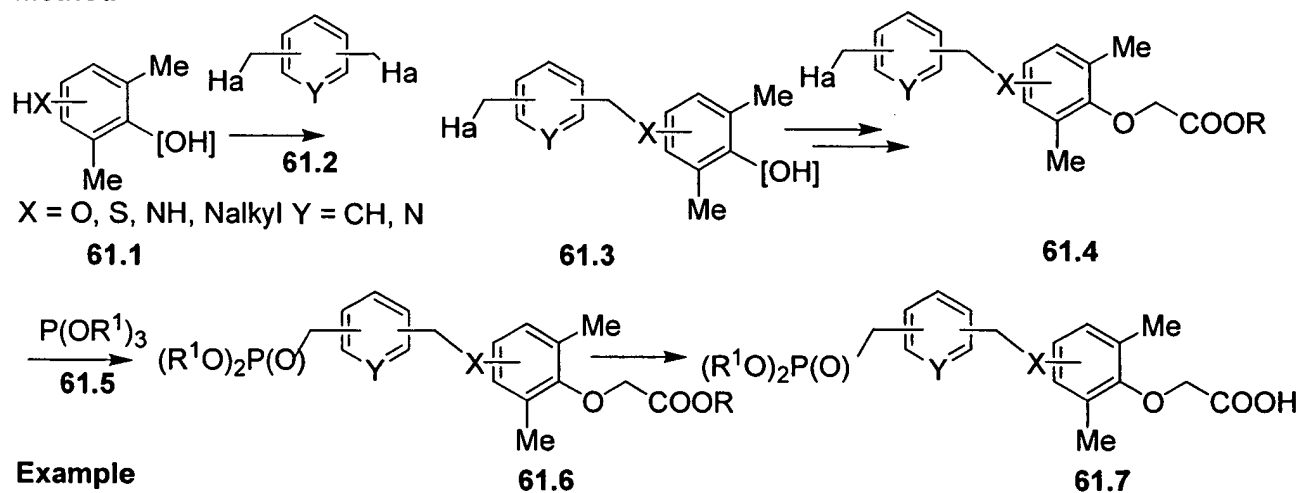


### Example

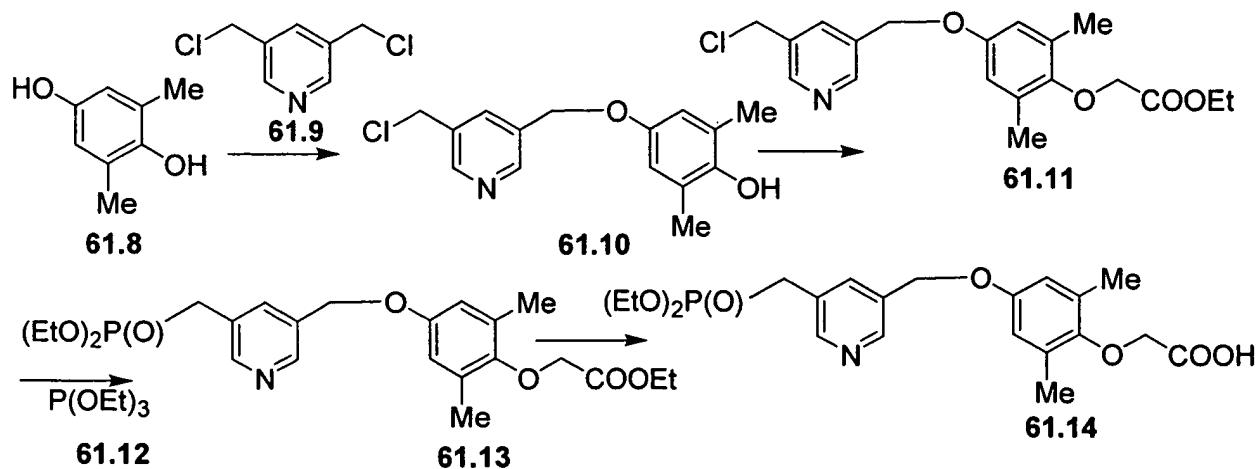


## Scheme 61

### Method



### Example



### Preparation of benzyl carbamate compounds incorporating phosphonate groups

Scheme 62 depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative C4 in which the phosphonate moiety is either directly attached to the phenyl ring or attached by means of an alkylene chain. In this procedure, a dialkyl hydroxymethylphenyl alkylphosphonate **62.1** is converted into an activated derivative **62.2**, in which Lv is a leaving group, as described above (Scheme 55). The product is then reacted with a suitably protected aminoacid **62.3**, to afford the carbamate product **62.4**. The reaction is conducted under the conditions described above for the preparation of carbamates (Scheme 55). The protecting group on the carboxylic acid group in the product **62.4** is then removed to afford the free carboxylic acid **62.5**. Methods for the protection and deprotection of carboxylic acids are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

For example, as shown in Scheme 62, Example 1, a dialkyl 4-hydroxymethylphenyl phosphonate **62.6**, prepared as described in US 5569664, is reacted with phosgene, or an equivalent thereof, as described above (Scheme 55), to afford the chloroformyl product **62.7**. This compound is then reacted in an inert solvent such as dichloromethane or tetrahydrofuran, with the tert. butyl aminoacid ester **62.3**, in the presence of a base such as triethylamine, to yield the carbamate product **62.8**. The conversion of acids into tert. butyl esters is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 245ff. The ester can be prepared by the reaction of the carboxylic acid with isobutylene and an acid catalyst, or by conventional esterification procedures employing tert. butanol. The tert. butyl protecting group is then removed from the product **62.8**, for example by reaction with trifluoroacetic acid at ambient temperature for about one hour, to afford the carboxylic acid **62.9**.

As a further example, Scheme 62, Example 2 shows the conversion of a dialkyl 4-hydroxymethyl benzyl phosphonate **62.10**, prepared as described in *J. Am. Chem. Soc.*, 1996, 118, 5881, into the hydroxybenztriazole derivative **62.11**. The reaction is performed as described above (Scheme 55). The activated derivative is then reacted with the aminoacid derivative **62.3**, as described above, to afford the carbamate **62.12**. deprotection, as previously described, then affords the carboxylic acid **62.13**.

Using the above procedures, but employing, in place of the phosphonates **62.6** and **62.10**, different phosphonates **62.1**, and/or different aminoacid derivatives **62.3**, the corresponding products **62.5** are obtained.

Scheme **63** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted benzyl alcohol **63.1** is subjected to a palladium catalyzed Heck reaction, as described above, (Scheme **26**) with a dialkyl alkenyl phosphonate **63.2**, to afford the olefinic product **63.3**. The product is then converted into the activated derivative **63.4**, which is then reacted with aminoacid derivative **62.3**, as described above, to afford, after deprotection of the carboxyl group, the carbamate product **63.5**. Optionally, the olefinic coupling product can be reduced to the saturated analog **63.6**. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 5. The product **63.6** is then converted, as described above, into the carbamate derivative **63.8**.

For example, 3-bromobenzyl alcohol **63.9** is coupled in acetonitrile solution, with a dialkyl allylphosphonate **63.10** (Aldrich), in the presence of palladium acetate, triethylamine and tri-*o*-tolylphosphine, as described in *Synthesis*, 1983, 556, to afford the product **63.11**. This material is then reacted with carbonyl diimidazole, as described above, (Scheme **55**) to afford the imidazolide **63.12**. The product is then coupled with the aminoacid derivative **62.3**, to afford after deprotection, the product **63.13**. Alternatively, the unsaturated phosphonate **63.11** is reduced, for example by reaction with diborane in tetrahydrofuran at ambient temperature, as described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 5., to afford the saturated analog **63.14**. The latter compound is then transformed, as described above, into the carbamate aminoacid derivative **63.15**.

Using the above procedures, but employing, in place of the 3-bromobenzyl alcohol **63.9**, different bromobenzyl alcohols **63.1**, and/or different alkenyl phosphonates **63.2**, and/or different amino acid derivatives, the corresponding products **63.5** and **63.8** are obtained.

Scheme **64** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of an amino-containing alkylene chain. In this procedure, a formyl-substituted

benzyl alcohol **64.1** is converted, using the procedures described above in Schemes **55** and **63**, into the aminoacid carbamate derivative **64.2**. The product is then subjected to a reductive amination reaction with a dialkyl aminoalkyl phosphonate **64.3**, to afford the phosphonate product **64.4**. Reductive amination of carbonyl compounds is described above (Scheme **27**).

For example, 3-formyl benzyl alcohol **64.5** is converted into the carbamate derivative **64.6**. The product is then reacted in ethanol solution at ambient temperature with a dialkyl aminoethyl phosphonate **64.7**, the preparation of which is described in *J. Org. Chem.*, 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the phosphonate product **64.8**.

Using the above procedures, but employing, in place of the 3-formylbenzyl alcohol **64.5**, different formylbenzyl alcohols **64.1**, and/or different aminoalkyl phosphonates **64.3**, the corresponding products **64.4** are obtained.

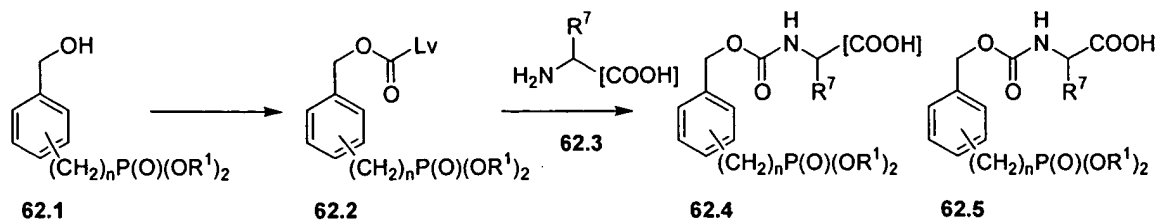
Scheme **65** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of an O, S or N-alkyl-containing alkylene chain. In this procedure, a chloromethyl-substituted benzyl alcohol **65.1** is reacted with a dialkyl hydroxy, mercapto or alkylaminoalkyl phosphonate **65.2**. The alkylation reaction is conducted between equimolar amounts of the reactants in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of an inorganic or organic base, such as diisopropylethylamine, dimethylaminopyridine, potassium carbonate and the like. The alkylated product **65.3** is then converted, as previously described, into the carbamate aminoacid derivative **65.4**.

For example, 4-chloromethylbenzyl alcohol **65.5**, (Aldrich) is reacted at ca. 60°C in acetonitrile solution with a dialkyl hydroxypropyl phosphonate **65.6**, the preparation of which is described in *Zh. Obshchei. Khim.*, 1974, 44, 1834, in the presence of dimethylaminopyridine, to afford the ether product **65.7**. The product is then converted, as previously described, into the carbamate derivative **65.8**.

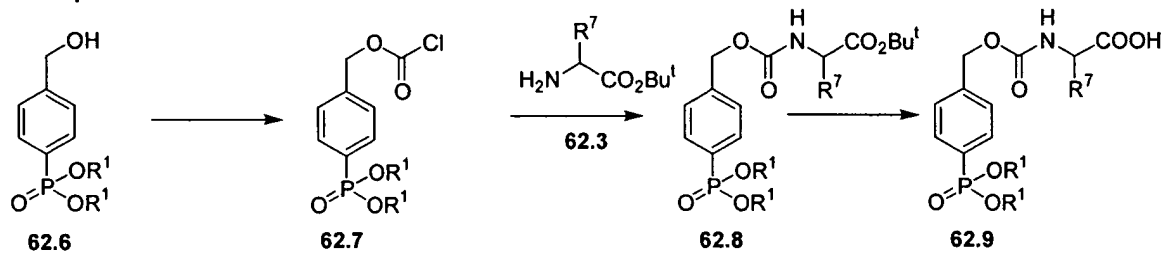
Using the above procedures, but employing, in place of 4-(chloromethyl)benzyl alcohol **65.5**, different chloromethyl benzyl alcohols **65.1**, and/or different hydroxy, mercapto or alkylamino phosphonates **65.2**, the corresponding products **65.4** are obtained.

Sch m 62

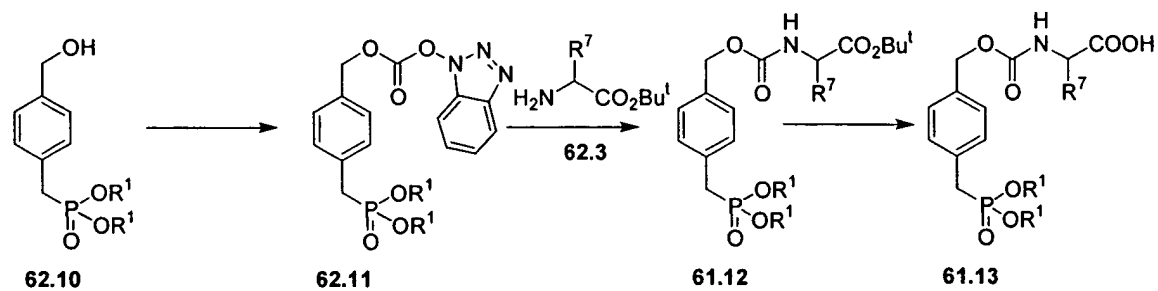
Method



Example 1

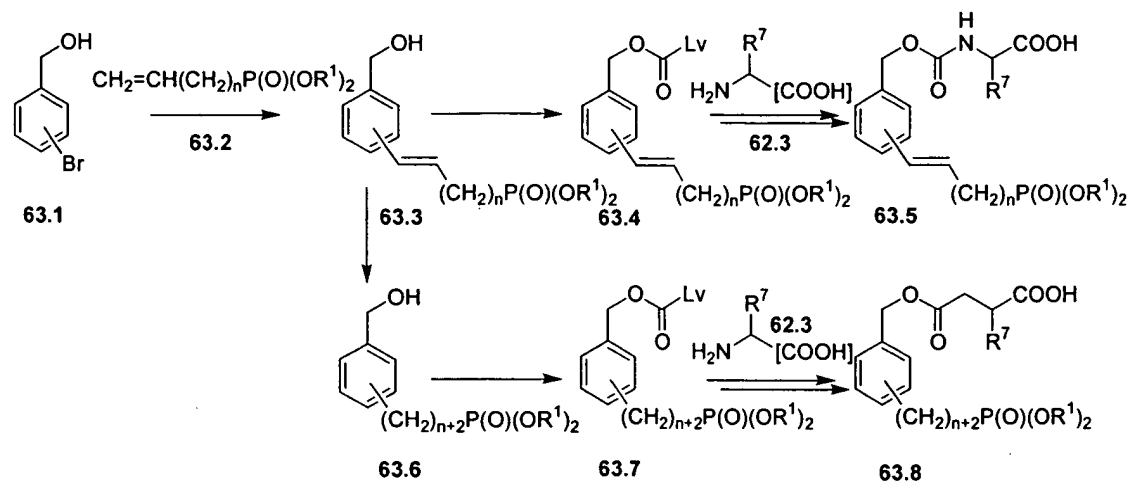


Example 2

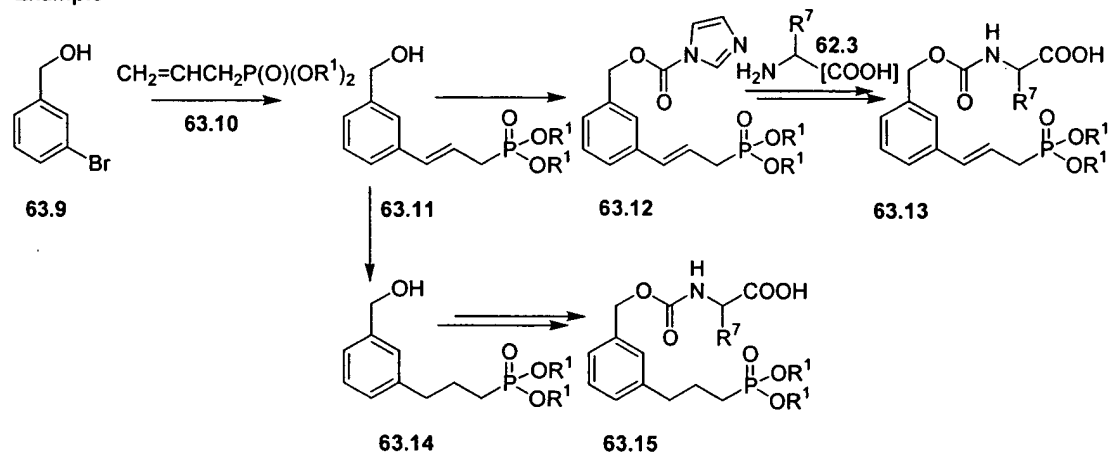


# Scheme 63

## Method

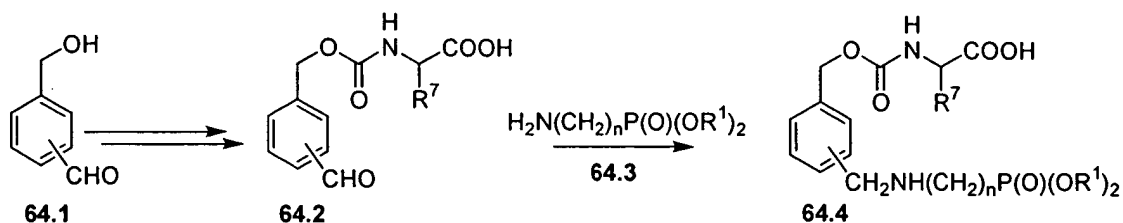


## Example

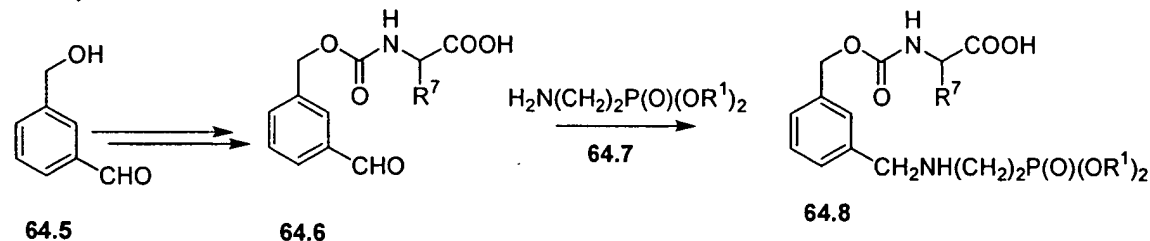


## Scheme 64

### Method

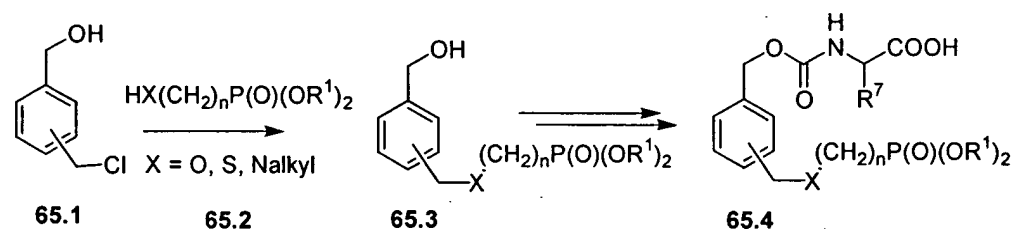


### Example

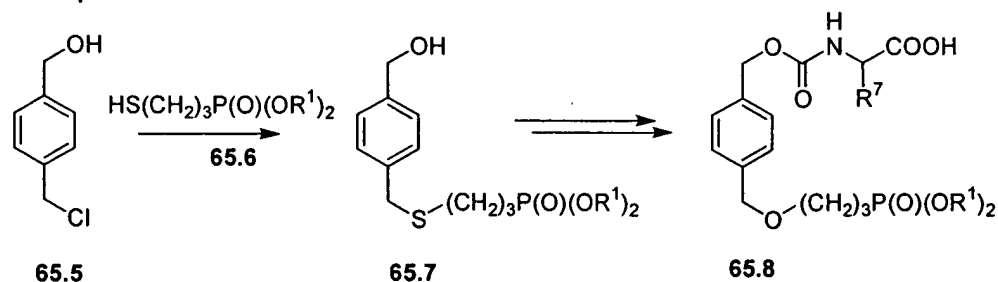


## Scheme 65

### Method



### Example



## Preparation of pyridinyloxymethyl piperidine derivatives incorporating phosphonate groups

Scheme 66 illustrates the preparation of phosphonate-containing analogs of the amine A12 in which the phosphonate moiety is attached to the pyridine ring by means of a heteroatom and an alkylene chain. In this procedure, 2-bromo-4-hydroxymethylpyridine, the preparation of which is described in *Chem. Pharm. Bull.*, 1990, 38, 2446, is subjected to a nucleophilic displacement reaction with a dialkyl hydroxy, thio or aminoalkyl-substituted alkyl phosphonate

**66.2.** The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2-bromopyridines by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100°C in the presence of a base such as potassium carbonate. The displacement product **66.3** is then converted into the activated derivative **66.4**, in which Lv is a leaving group such as halo, methanesulfonyloxy, p-toluenesulfonyloxy and the like. The conversion of alcohols into chlorides and bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols can be transformed into the chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in *J. Am. Chem. Soc.*, 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in *J. Am. Chem. Soc.*, 92, 2139, 1970. Alcohols can be converted into sulfonate esters by treatment with the alkyl or aryl sulfonyl chloride and a base, in a solvent such as dichloromethane or pyridine. Preferably, the carbinol **66.3** is converted into the corresponding chloro compound, **66.4**, in which Lv is Cl, as described above. The product is then reacted with the piperidinol derivative **66.5**. The preparation of the compounds **66.5** is described in U.S. 5,614,533, and in *J. Org. Chem.*, 1997, 62, 3440. The piperidinol derivative **66.5** is treated in dimethylformamide with a strong base such as sodium hydride, and the alkylating agent **66.4** is then added. The reaction proceeds to afford the ether product **66.6**, and the BOC protecting group is then removed to yield the free amine compound **66.7**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate **66.6** with hydrochloric acid, as described in *J. Org. Chem.*, 1997, 62, 3440.

For example, 2-bromo-4-hydroxymethylpyridine **66.1** the preparation of which is described in *Chem. Pharm. Bull.*, 1990, 38, 2446, is reacted in dimethylformamide solution at ca 80°C with an equimolar amount of a dialkyl mercaptoethyl phosphonate **66.8**, prepared as described in *Zh. Obschei. Khim.*, 1973, 43, 2364, and potassium carbonate, to yield the thioether

product **66.9**. The product is then reacted with one molar equivalent of methanesulfonyl chloride in pyridine at 0°C, to produce the mesylate compound **66.10**. This material is reacted with the piperidinol reagent **66.5**, using the conditions described above, to afford the ether **66.11**. The BOC protecting group is then removed as previously described, to afford the amine product **66.12**.

Using the above procedures, but employing, in place of the mercaptoethyl phosphonate **66.8**, different hydroxy, mercapto or alkylamino phosphonates **66.2**, the corresponding products **66.7** are obtained.

Scheme **67** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is directly attached to the pyridine ring. In this procedure, a bromo-substituted 4-hydroxymethylpyridine **67.1** is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **67.2**. The reaction between aryl bromides and dialkyl phosphites to yield aryl phosphonates is described in *Synthesis*, 56, 1981, and in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The thus-obtained pyridylphosphonate **67.3** is then converted, as described above (Scheme **66**) into an activated derivative **67.4**, and the latter compound is transformed as described above into the amine **67.5**.

For example, 3-bromo-4-hydroxymethylpyridine **67.5**, prepared as described in *Bioorg. Med. Chem. Lett.*, 1992, 2, 1619, is reacted with a dialkyl phosphite **67.2**, as described above, to prepare the phosphonate **67.7**. The product is then transformed into the chloro derivative by reaction with triphenylphosphine and N-chlorosuccinimide, and the product is converted, as described above (Scheme **66**) into the amine **67.9**.

Using the above procedures, but employing, in place of the 3-bromopyridine derivative **67.6**, different bromopyridines **67.1**, and/or different phosphites, the corresponding products **67.5** are obtained.

Scheme **68** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of an amine group and an alkyl chain. In this procedure, an amino-substituted 4-hydroxymethylpyridine **68.1** is subjected to a reductive amination reaction with a dialkyl formylalkyl phosphonate **68.2**. The preparation of amines by means of reductive amination procedures is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The amine product **68.3** is then converted, as described above, into the piperidine derivative **68.5**.

For example, 2-amino-4-hydroxymethylpyridine **68.6**, prepared as described in *Aust. J. Chem.*, 1993, 46, 9897, is reacted in ethanol solution with a dialkyl formylmethylphosphonate **68.7**, prepared as described in *Zh. Obschei. Khim.*, 1987, 57, 2793, in the presence of sodium cyanoborohydride, to yield the amine product **68.8**. This material is then transformed into the chloro derivative **68.9** by reaction with hydrogen chloride in ether. The chloro product is then transformed, as described above, into the piperidine derivative **68.10**.

Using the above procedures, but employing, in place of the 2-aminopyridine derivative **68.6**, different aminopyridines **68.1**, and/or different formylalkyl phosphonates **68.2** the corresponding products **68.5** are obtained.

Scheme 69 illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of a saturated or unsaturated alkyl chain. In this procedure, a bromo-substituted 4-hydroxymethylpyridine **69.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **69.2**. The coupling of aryl bromides and olefins is described above (Scheme 26). The product is then converted, as described above, into the piperidine derivative **69.5**. Optionally, the latter compound can be reduced, for example as described above in Scheme 26, to afford the saturated analog **69.6**.

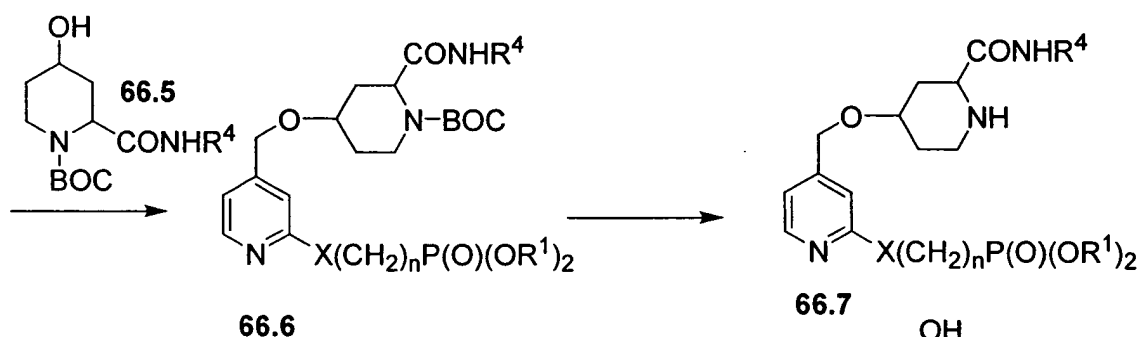
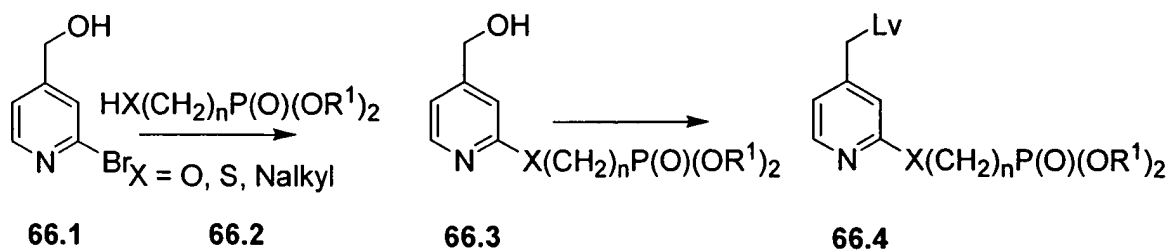
For example, 3-bromo-4-hydroxymethylpyridine **69.7**, prepared as described in *Bioorg. Med. Chem. Lett.*, 1992, 2, 1619, is coupled with a dialkyl vinylphosphonate **69.8**, prepared as described in *Synthesis*, 1983, 556, to yield the olefinic product **69.9**. The product is reacted with one molar equivalent of p-toluenesulfonyl chloride in pyridine at ambient temperature to afford the tosylate **69.10**. The latter compound is then transformed, as previously described, into the

piperidine derivative **69.11**. Optionally, the latter compound is reduced, for example by reaction with diimide, to yield the saturated analog **69.12**.

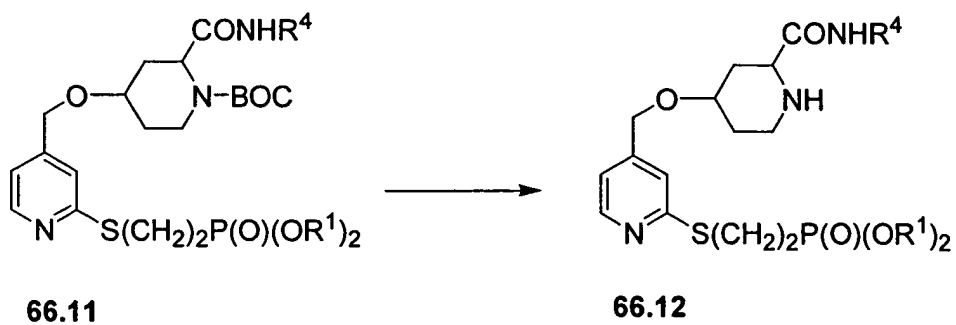
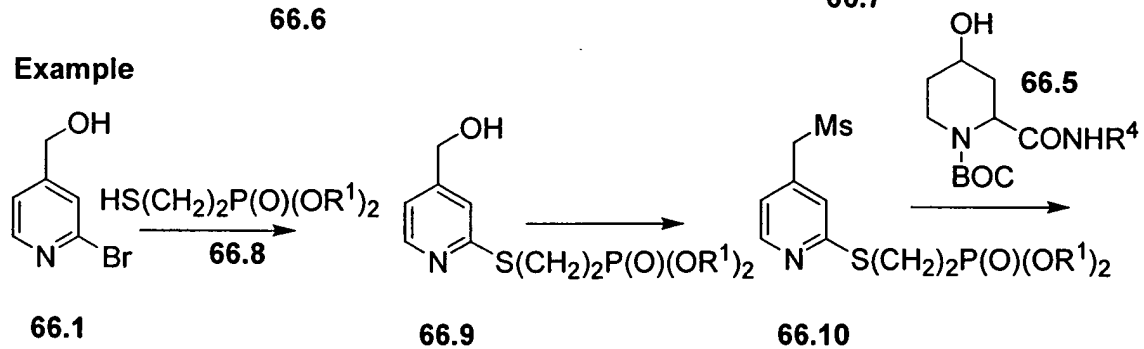
Using the above procedures, but employing, in place of the 3-bromopyridine derivative **69.7**, different bromopyridines **69.1**, and/or different alkenyl phosphonates **69.2** the corresponding products **69.5** and **69.6** are obtained.

# Scheme 66

## Method

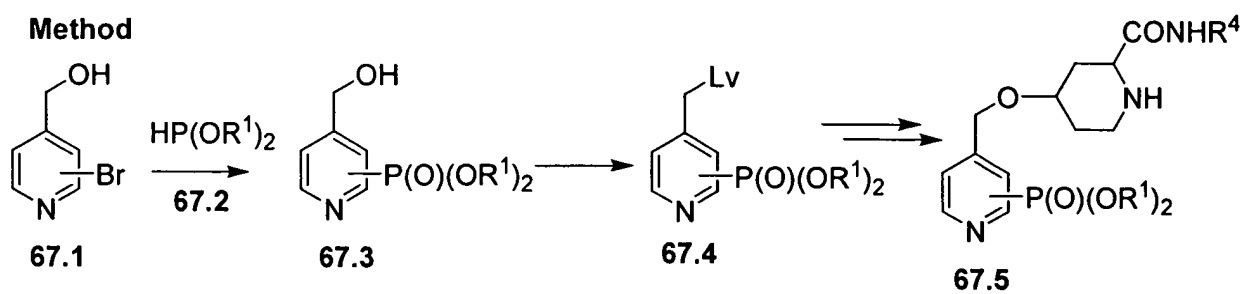


## Example

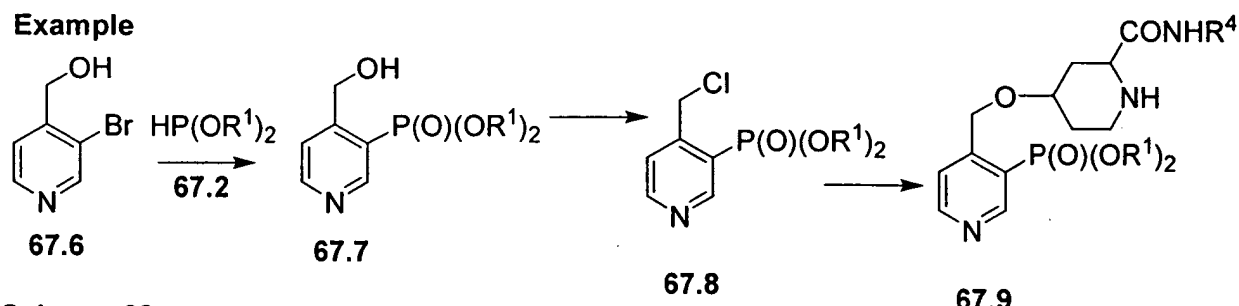


# Scheme 67

## Method

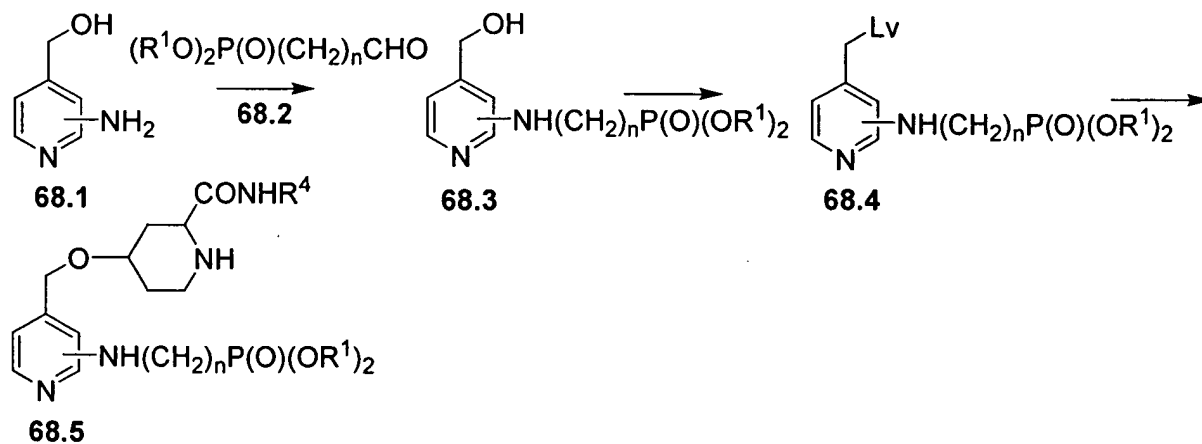


## Example

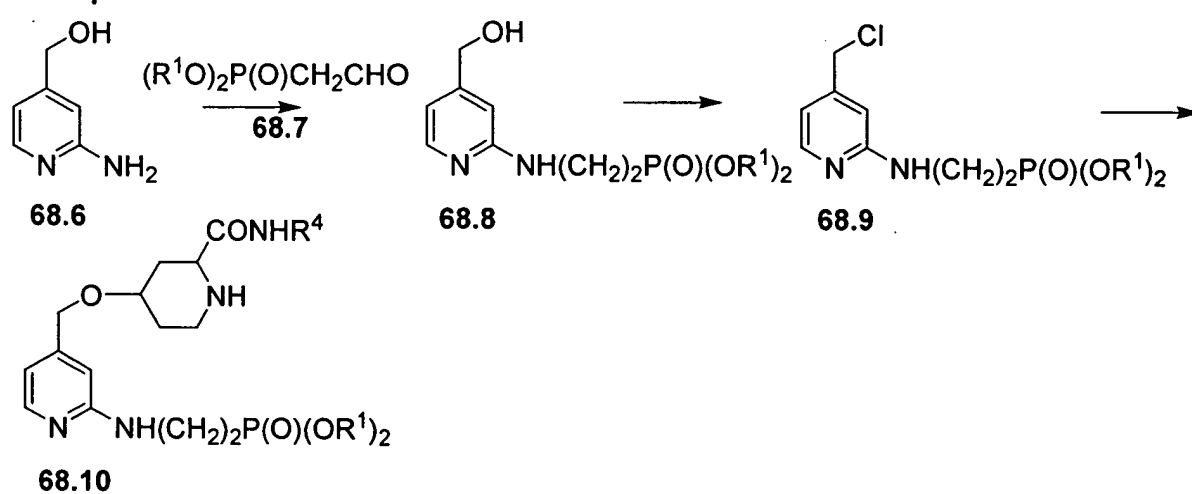


# Scheme 68

## Method

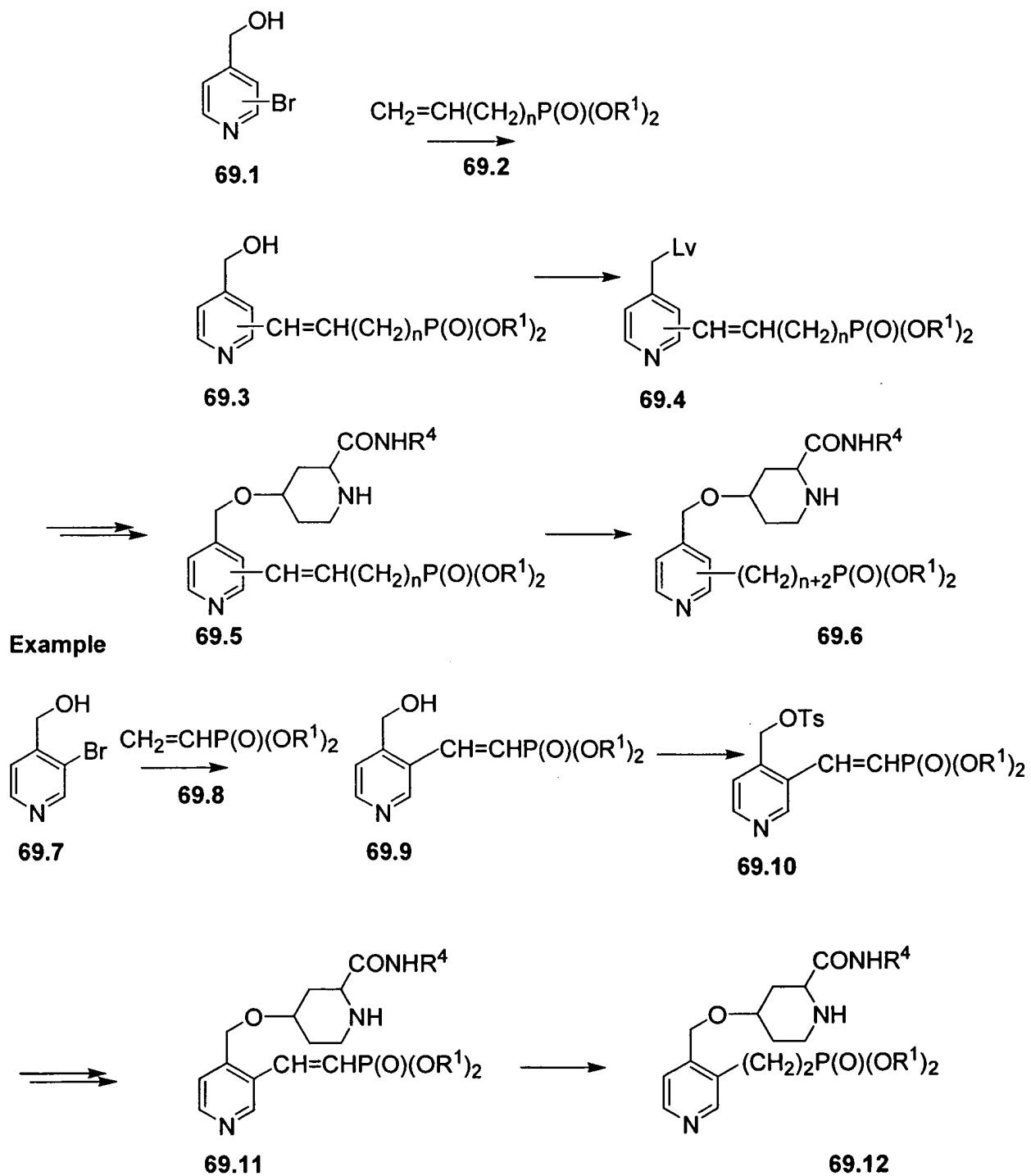


## Example



# Scheme 69

## Method



### **General applicability of methods for introduction of phosphonate substituents**

The procedures described herein for the introduction of phosphonate moieties are, with appropriate modifications, transferable to different chemical substrates. For example, the methods described above for the introduction of phosphonate groups into the quinoline-2-carboxylic moiety (Schemes 24-27), can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine, thiophenol, tert-butylamine and decahydroisoquinoline moieties. Similarly, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety (Schemes 28-34), the thiophenol moiety (Schemes 35-44) the tert-butylamine moiety (Schemes 45-48), decahydroisoquinoline moiety (Schemes 48a-52), dimethylphenoxyacetic acids (Schemes 56 - 61), benzyl carbamates (Schemes 62 - 65) and pyridines (Schemes 66 - 69) can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the quinoline-2-carboxylic acid component.

### **Preparation of (Pyridin-3-yloxy)-acetic acids incorporating phosphonate moieties**

Scheme 70 illustrates two alternative methods by means of which (pyridin-3-yloxy)-acetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the pyridyl moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed (Pyridin-3-yloxy)-acetic acid intermediate. In the first sequence, a substituted 3-hydroxypyridine 70.1, in which the substituent B is a precursor to the group  $\text{link-P(O)(OR}^1\text{)}_2$ , and in which the aryl hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound 70.2. Methods for the conversion of the substituent B into the group  $\text{link-P(O)(OR}^1\text{)}_2$  are described in Schemes 25 - 75.

The protected aryl hydroxyl group present in the phosphonate-containing product 70.2 is then deprotected, using methods described below, to afford the phenol 70.3.

The product 70.3 is then transformed into the corresponding (pyridin-3-yloxy) acetic acid 70.4, in a two step procedure. In the first step, the phenol 70.3 is reacted with an ester of bromoacetic acid 70.9, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of aryl hydroxyl groups to afford aryl ethers is described, for example, in Comprehensive Organic

Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the aryl reagent and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **70.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in U.S. Patent 5,914,332, to afford the ester **70.4**.

The thus-obtained ester **70.4** is then hydrolyzed to afford the carboxylic acid **70.5**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product **70.4** which R is ethyl is hydrolyzed to the carboxylic acid **70.5** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in U.S. Patent 5,914,332.

Alternatively, an appropriately substituted 3-hydroxypyridine **70.6**, in which the substituent B is a precursor to the group  $\text{link-P(O)(OR}^1)_2$ , is transformed into the corresponding acetic acid ester **70.7**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **70.3** into the ester **70.4**.

The acetic acid ester **70.7** is then converted into the carboxylic acid **70.5** using the 2 step procedure shown above, involving transformation of the group B into the group  $\text{link-P(O)(OR}^1)_2$  followed by ester hydrolysis of the acetic acid ester. The group B which is present in the ester **70.7** may be transformed into the group  $\text{link-P(O)(OR}^1)_2$  either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **70-75** illustrate the preparation of (Pyridin-3-yloxy)-acetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of acetic esters acids **70.7**, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme 71 depicts the preparation of (pyridin-3-yloxy) acetic acids incorporating a phosphonate group linked to the pyridyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected halo-substituted 3-hydroxypyridine **71.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **71.2**. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl halide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **71.3** is converted, using the procedures described above, (Scheme 70) into the corresponding (pyridin-3-yloxy) acetic acid **71.4**. Alternatively, the olefinic product **71.3** is reduced to afford the saturated derivative **71.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product **71.5** is converted, as described above, (Scheme 70) into the corresponding (pyridin-3-yloxy) acetic acid **71.6**.

For example, 2-iodo-5-hydroxy pyridine **71.7**, prepared as described in *J. Org. Chem.*, 1990, 55, 18, p. 5287, is converted into the tert-butyldimethylsilyl ether **71.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **71.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **71.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°C, to produce the coupled product **71.10**. Alternatively see *J. Med. Chem.* 1999, 42, 4, p. 669 for alternative conditions for this reaction. The silyl group is removed, for example by the treatment of the ether **71.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972, to afford the phenol **71.11**. This compound is converted, employing the procedures described above, (Scheme 70) into the corresponding (pyridin-3-yloxy) acetic acid **71.12**. Alternatively, the unsaturated compound **71.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N.

Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **71.13**. This compound is converted, employing the procedures described above, (Scheme 70) into the corresponding (pyridin-3-yloxy) acetic acid **71.14**.

Using the above procedures, but employing, in place of 2-iodo-5-hydroxy pyridine **71.7**, different iodo or bromohydroxypyridines **71.1**, and/or different dialkyl alkenyl phosphonates **71.2**, the corresponding products **71.4** and **71.6** are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described above (Scheme 54).

Scheme 72 illustrates the preparation of phosphonate-containing analogs of (pyridin-3-yloxy) acetic acids in which the phosphonate moiety is attached to the pyridine ring by means of a heteroatom and an alkyl chain. In this procedure, a suitably protected 2-halo-5-hydroxypyridine, (see Scheme 71) is subjected to a nucleophilic displacement reaction with a dialkyl hydroxy, thio or aminoalkyl-substituted alkyl phosphonate **72.2**. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2-bromopyridines, by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100°C in the presence of a base such as potassium carbonate. The displacement product **72.3** is then converted into the hydroxyl derivative **72.4** and then into the (pyridin-3-yloxy) acetic acid phosphonate ester **72.5** using the procedures described above (Scheme 70).

For example, 2-iodo-5-hydroxypyridine **71.7** (Scheme 71) is treated with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **72.6**. The benzyl ether **72.6** is reacted in dimethylformamide solution at ca 80°C with an equimolar amount of a dialkyl mercaptoethyl phosphonate **72.7**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **72.8**. The benzyl group is then removed by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.

266ff., to afford the hydroxyl compound **72.9**. The product **72.9** is then converted into the (pyridin-3-yloxy) acetic acid phosphonate ester **72.10** using the procedures described above (Scheme 70).

Using the above procedures, but employing, in place of the mercaptoethyl phosphonate **72.7**, different hydroxy, mercapto or alkylamino phosphonates **72.2**, and/or in place of the pyridine **71.7** different halo pyridines **71.1**, the corresponding products **72.5** are obtained.

Scheme 73 illustrates the preparation of phosphonate-containing analogs of (pyridin-3-yloxy) acetic acids in which the phosphonate moiety is directly attached to the pyridine ring. In this procedure, a suitably protected 2-bromo-5-hydroxypyridine **73.1** is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **73.2**. The reaction between aryl bromides and dialkyl phosphites to yield aryl phosphonates is described in *Synthesis*, **70**, 1981, and in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The thus-obtained pyridylphosphonate **73.3** is then converted, as described above (Scheme 72) into the (pyridin-3-yloxy) acetic acid phosphonate ester **73.5**.

For example, 3-bromo-5-hydroxypyridine **73.6** (Synchem-OHG) is treated with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **73.7**. The product **73.7** is then treated with a dialkylphosphite **73.2** as described above to give the phosphonate **73.8**. Employing the conditions described above (Scheme 72) **73.8** is converted in several steps to the (pyridin-3-yloxy) acetic acid phosphonate ester **73.10**.

Using the above procedures, but employing, in place of the 3-bromopyridine derivative **73.6**, different bromopyridines **73.1**, and/or different phosphites, the corresponding products **73.5** are obtained.

Scheme 74 illustrates the preparation of (pyridin-3-yloxy) acetic acids incorporating a phosphonate group attached to the pyridyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an hydroxy, thio or amino-substituted 3-hydroxy pyridine **74.1**, protected at the 3-hydroxyl position is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl

phosphonate **74.6**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°C. The product of the alkylation reaction, **74.2** is then converted, as described above for converting **72.3** to **72.5** (Scheme 72) into the acid **74.5**.

Alternatively, the protected pyridine **74.7** is converted to the acetic acid ester derivative **74.8** using the procedures described above in Scheme 70. The acetic acid ester **74.8**, is then deprotected following the procedures described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch 3,6, and 7, and the product treated with a dialkyl bromoalkyl phosphonate **74.6** to give **74.4**. The ester **74.4** is converted to the acid **74.5** using the procedures described above (Scheme 70).

For example, 3-benzyloxy, 5-hydroxy pyridine **74.10**, prepared as described *Bioorg and Med. Chem. Lett.* 1998, p. 2797, is converted to the ester **74.11** by treatment with ethylbromoacetate as described above (Scheme 70). The benzyl group is removed, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the hydroxy pyridine **74.12**. The product **74.12** is reacted in dimethylformamide at ca. 60°C with an equimolar amount of a dialkyl bromobutyl phosphonate **74.14**, the preparation of which is described in *Synthesis*, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the phosphonate ether product **74.13**. This compound is converted, employing the procedures described above, (Scheme 70) into the corresponding acid **74.15**.

Using the above procedures, but employing, in place of the pyridine **74.10**, different hydroxy, thio or aminophenols **74.1**, and/or different dialkyl bromoalkyl phosphonates **74.6**, the corresponding products **74.5** are obtained.

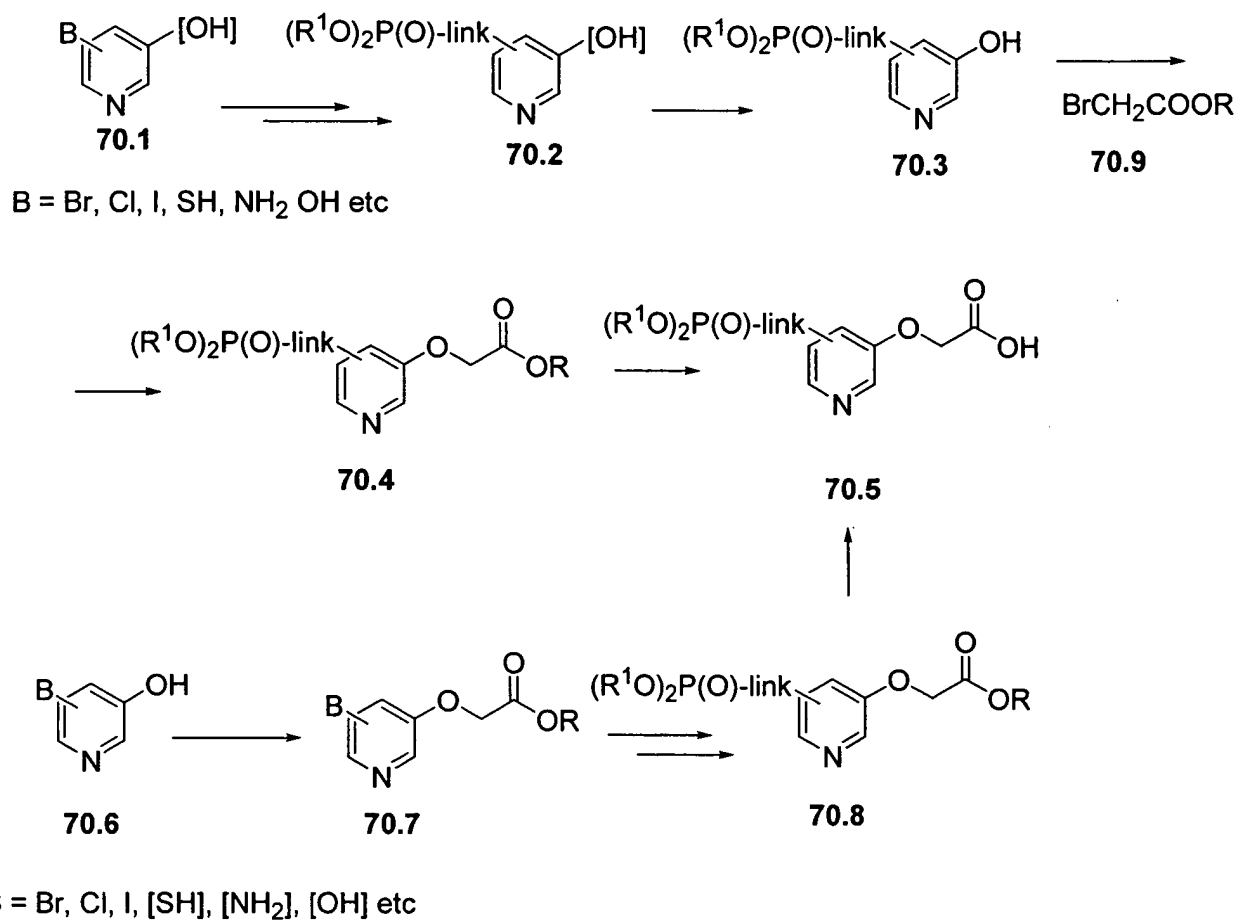
Scheme 75 illustrates the preparation of (Pyridin-3-yloxy)-acetic acids incorporating a phosphonate ester which is attached to the pyridyl group by means of a carbon chain incorporating a nitrogen atom. The compounds **75.4** are obtained by means of a reductive alkylation reaction between hydroxyl protected 3-hydroxypyridyl aldehyde **75.1** and an aminoalkyl phosphonate ester **75.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component **75.2** and the aldehyde component

**75.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **75.3**. The amination product **75.3** is then deprotected according to procedures described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch3, and subsequently converted into the (pyridin-3-yloxy) acetic acid compound **75.4**, using the alkylation and ester hydrolysis procedures described above (Scheme 70).

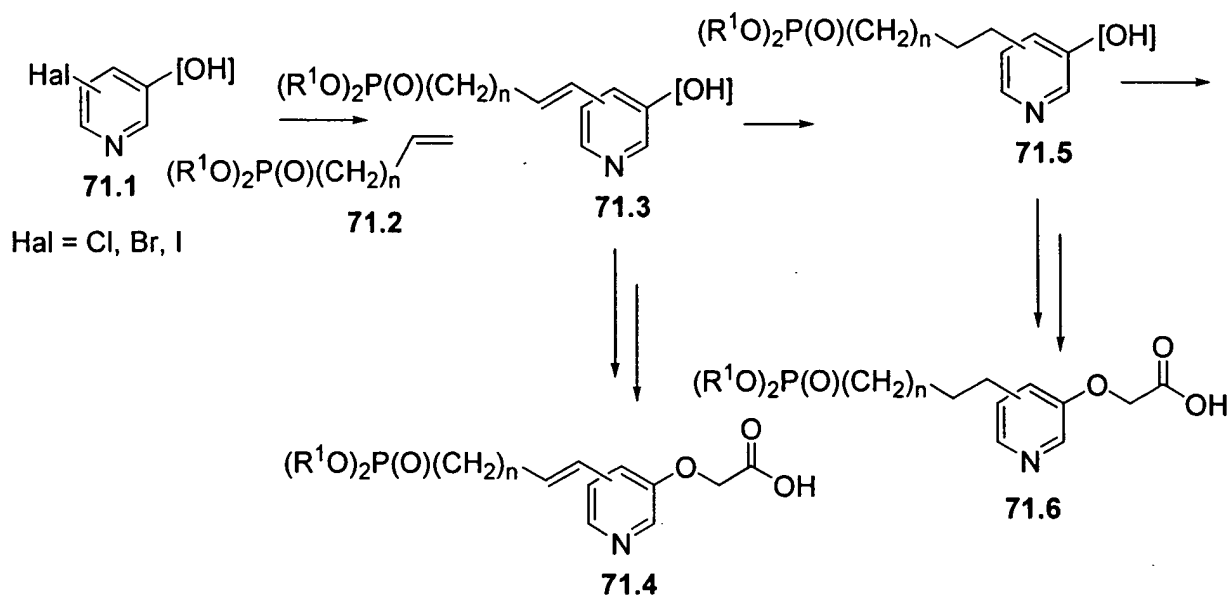
For example, the ester **75.5** (TCI-US) is reacted with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **75.6**. The benzyl ether **75.6** is then converted to the aldehyde **75.7** by reaction with DIBAL (see Comprehensive Organic Transformations, by R. C. Larock, 2<sup>nd</sup> Edition, 1999, p. 1267. for examples). Equimolar amounts of aldehyde **75.7**, and a dialkyl aminoethyl phosphonate **75.8**, the preparation of which is described in *J. Org. Chem.*, 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in *J. Amer. Chem. Soc.*, 91, 3996, 1969, to afford the amine product **75.9**. The benzyl group is then removed by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the hydroxyl compound **75.10**. The product **75.10** is then converted into the acetic acid **75.11**, as described above (Scheme 70).

Using the above procedures, but employing, in place of the aldehyde **75.7**, different aldehydes **75.1**, and/or different aminoalkyl phosphonates **75.2**, the corresponding products **75.4** are obtained.

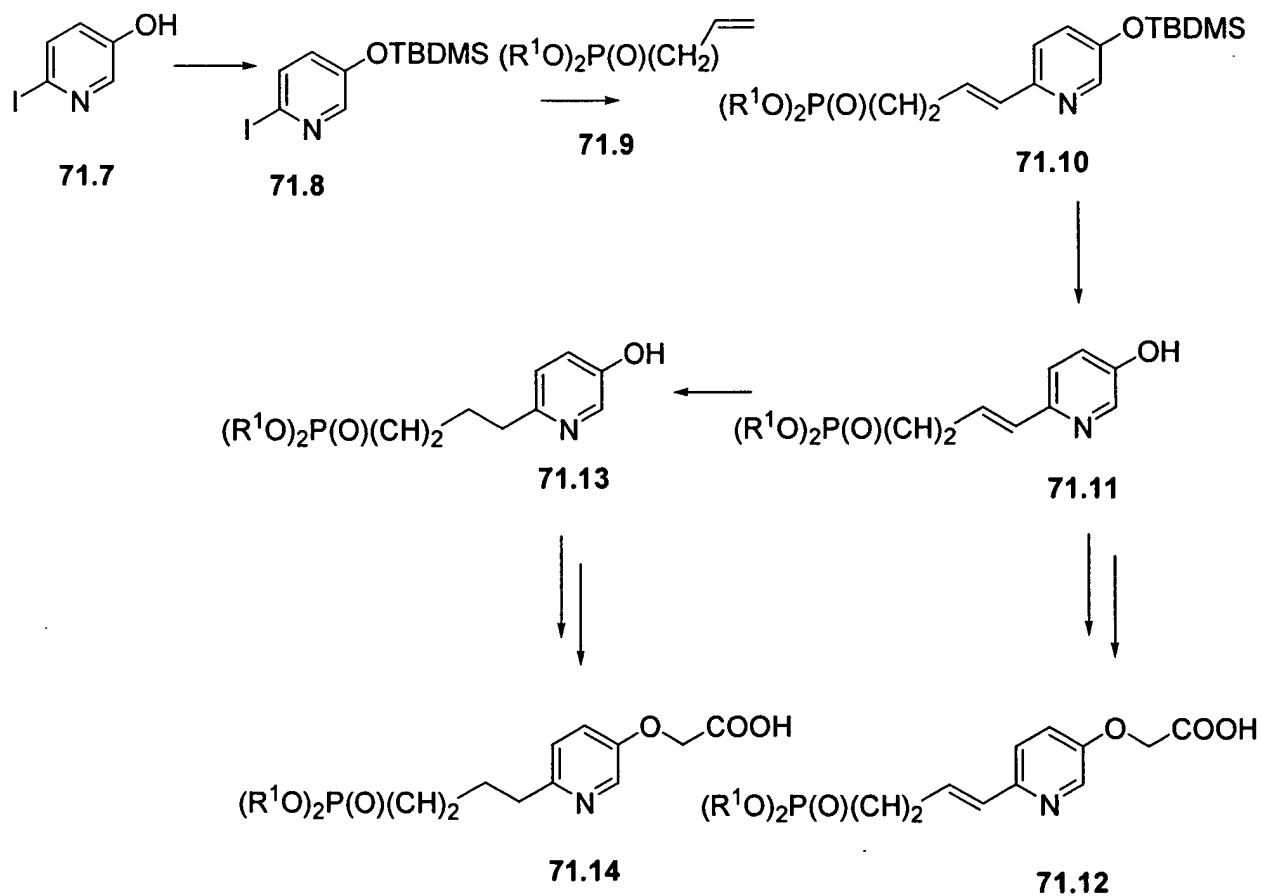
**Scheme 70**



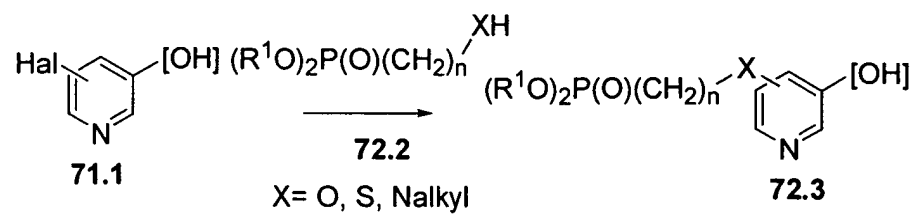
Scheme 71



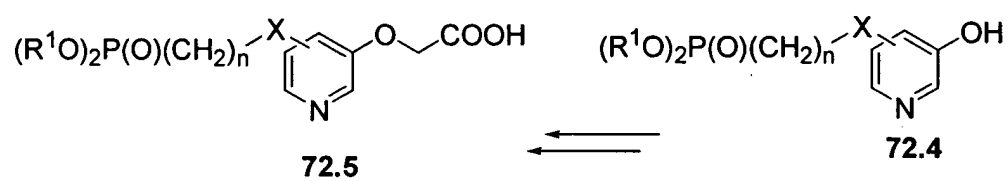
Example



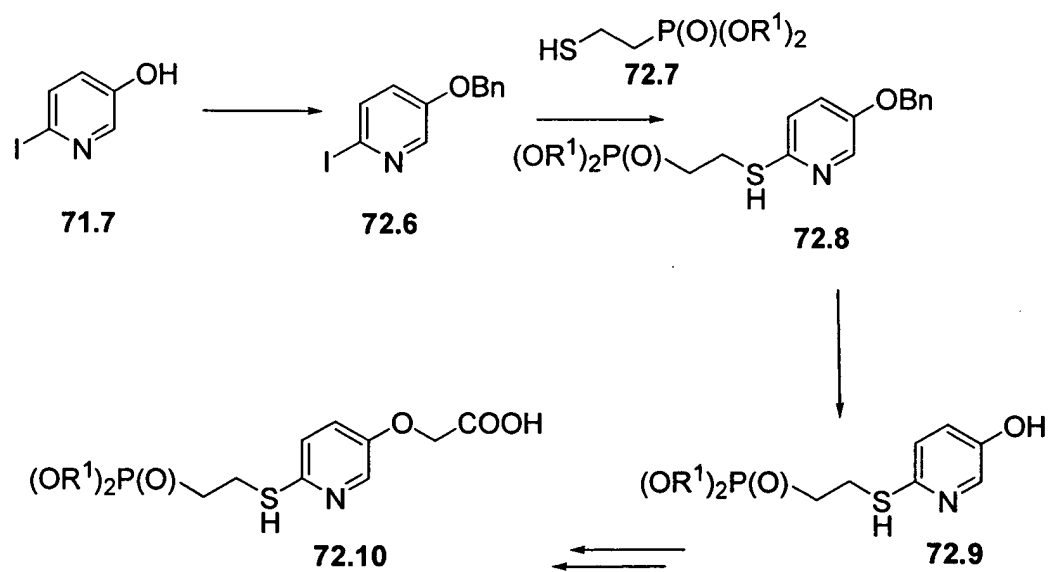
# **Scheme 72**



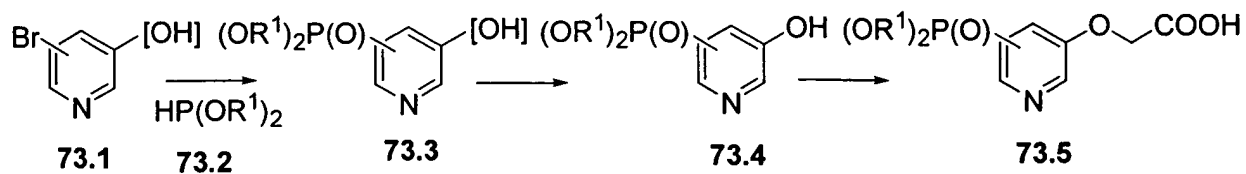
Hal = Cl, Br, I



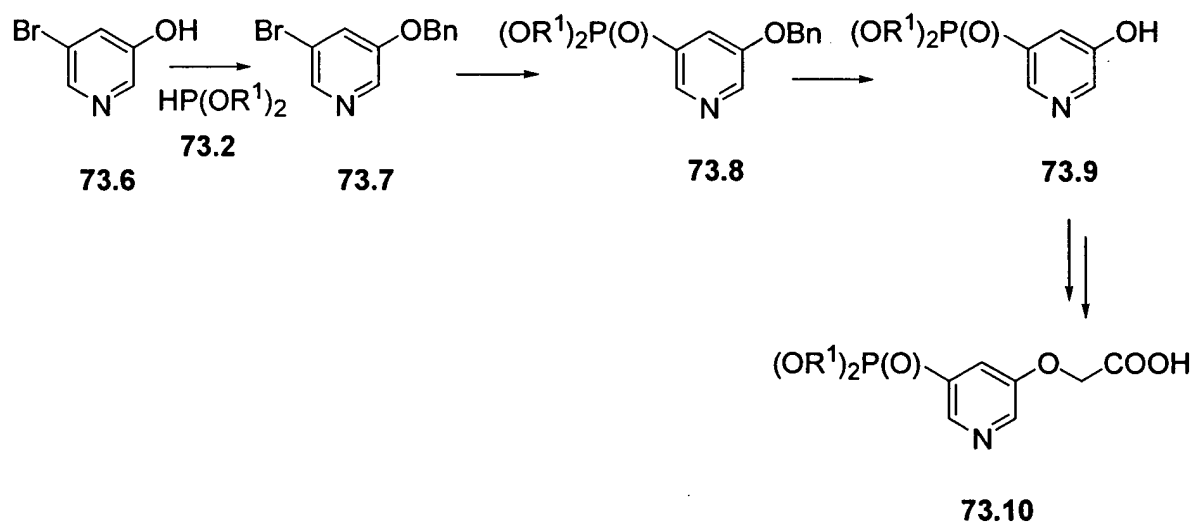
## **Example**



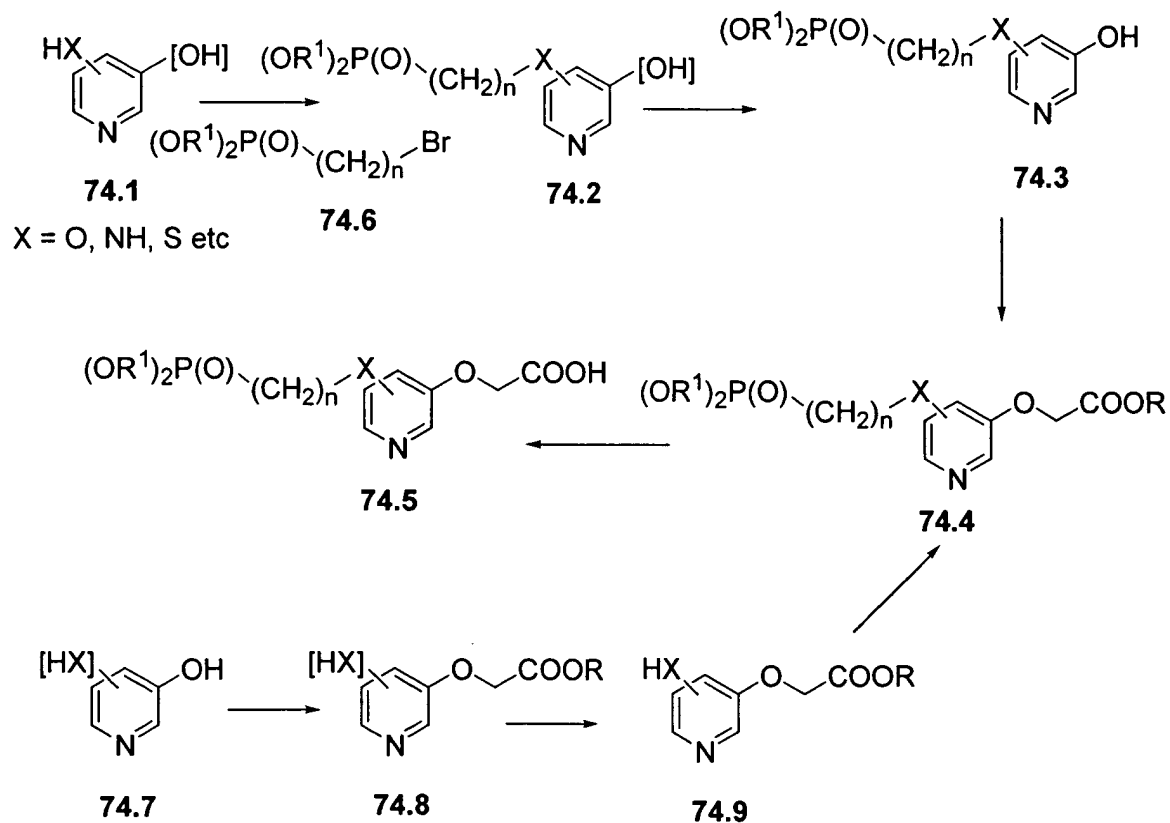
### Scheme 73



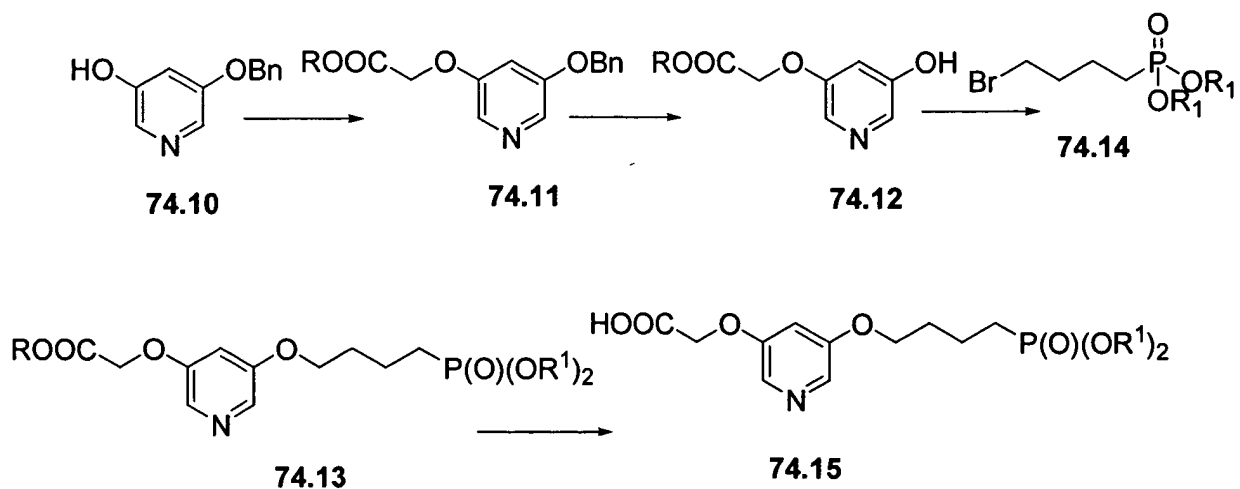
### Example



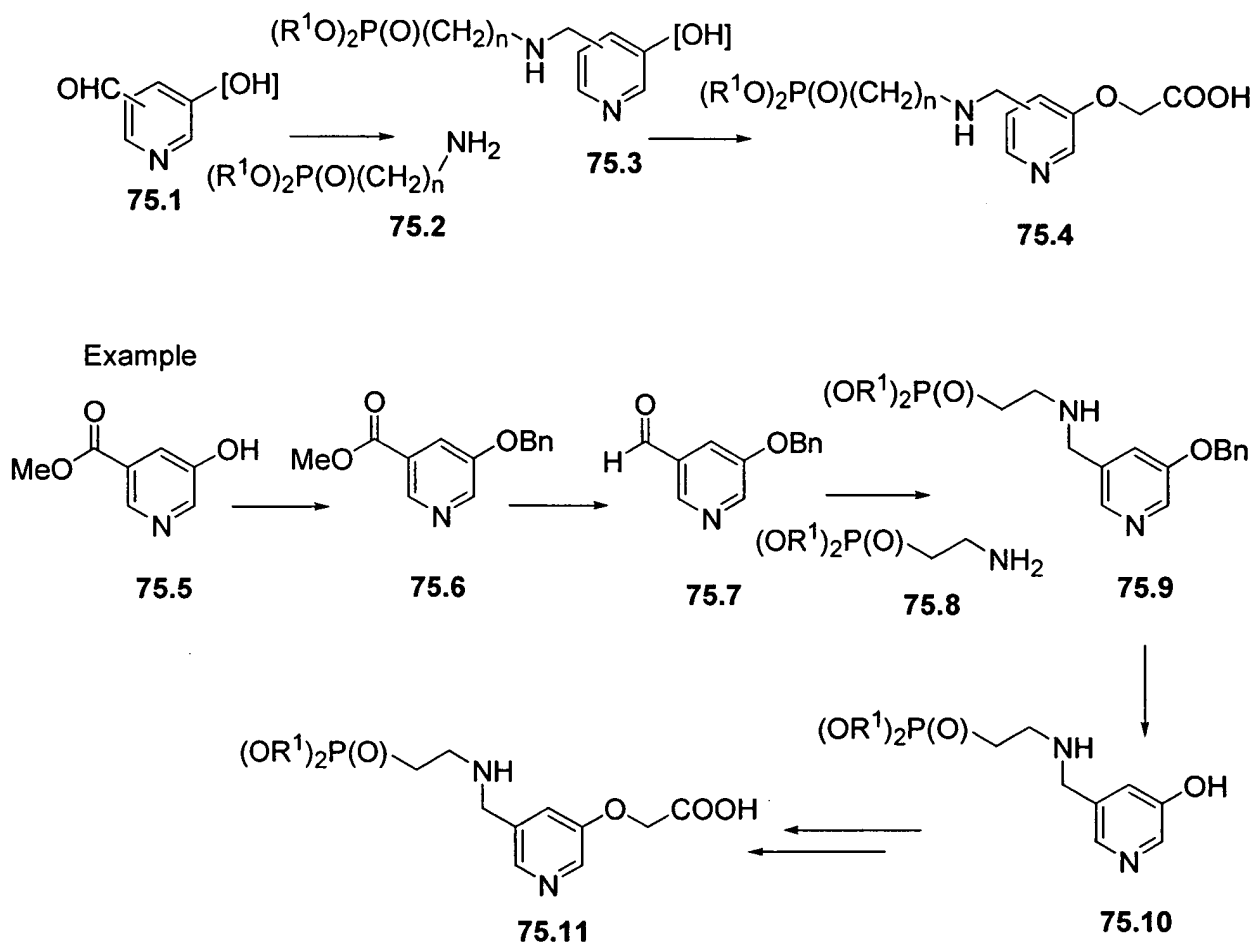
# Scheme 74



## Example



**Scheme 75**



### Ritonavir-like phosphonate protease inhibitors (RLPPI)

#### **Chemistry for Ritonavir analogs**

#### **Preparation of the intermediate phosphonate esters**

The structures of the intermediate phosphonate esters **1** to **7**, and the structures for the component groups  $R^1$  of this invention are shown in Chart 1. The structures of the components  $R^2COOH$ ,  $R^3COOH$  and  $R^4$  are shown in Charts **2a**, **2b** and **2c**. Specific stereoisomers of some of the structures are shown in Charts 1 and 2; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **7**. Subsequent chemical modifications to the compounds **1** to **7**, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds **1** to **7** incorporate a phosphonate moiety connected to the nucleus by means of a variable linking group, designated as “link” in the attached structures. Charts **3** and **4** illustrate examples of the linking groups present in the structures **1** – **7**, and in which “etc” refers to the scaffold, *e.g.*, ritonavir.

Schemes **1** - **28** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1**- **5**, and of the intermediate compounds necessary for their synthesis. The preparation of the compounds **6** and **7**, in which the phosphonate moiety is attached to the  $R^2COOH$  or  $R^3COOH$  group, is also described below.

Chart 1 Structures of the intermediate phosphonate esters 1-7

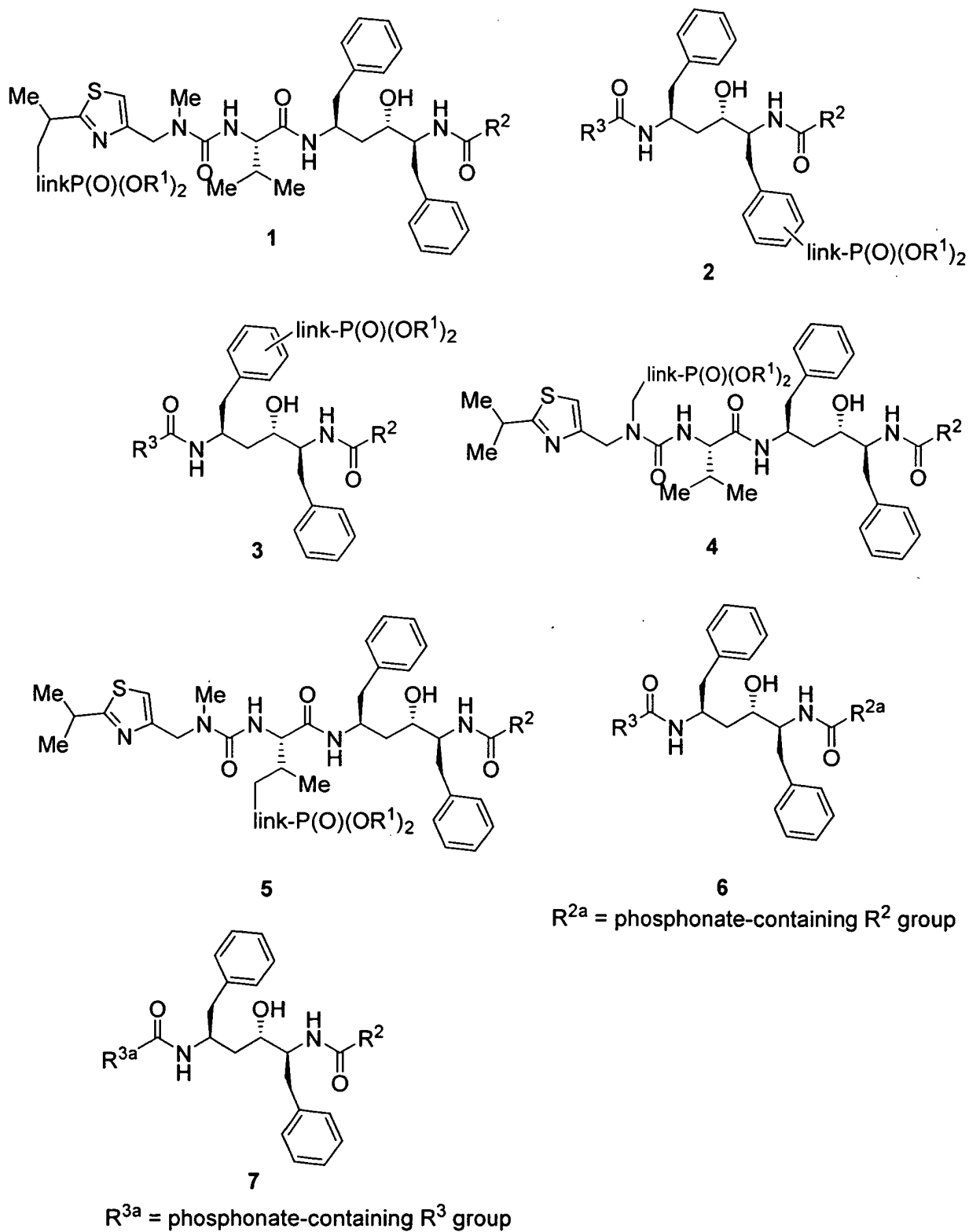
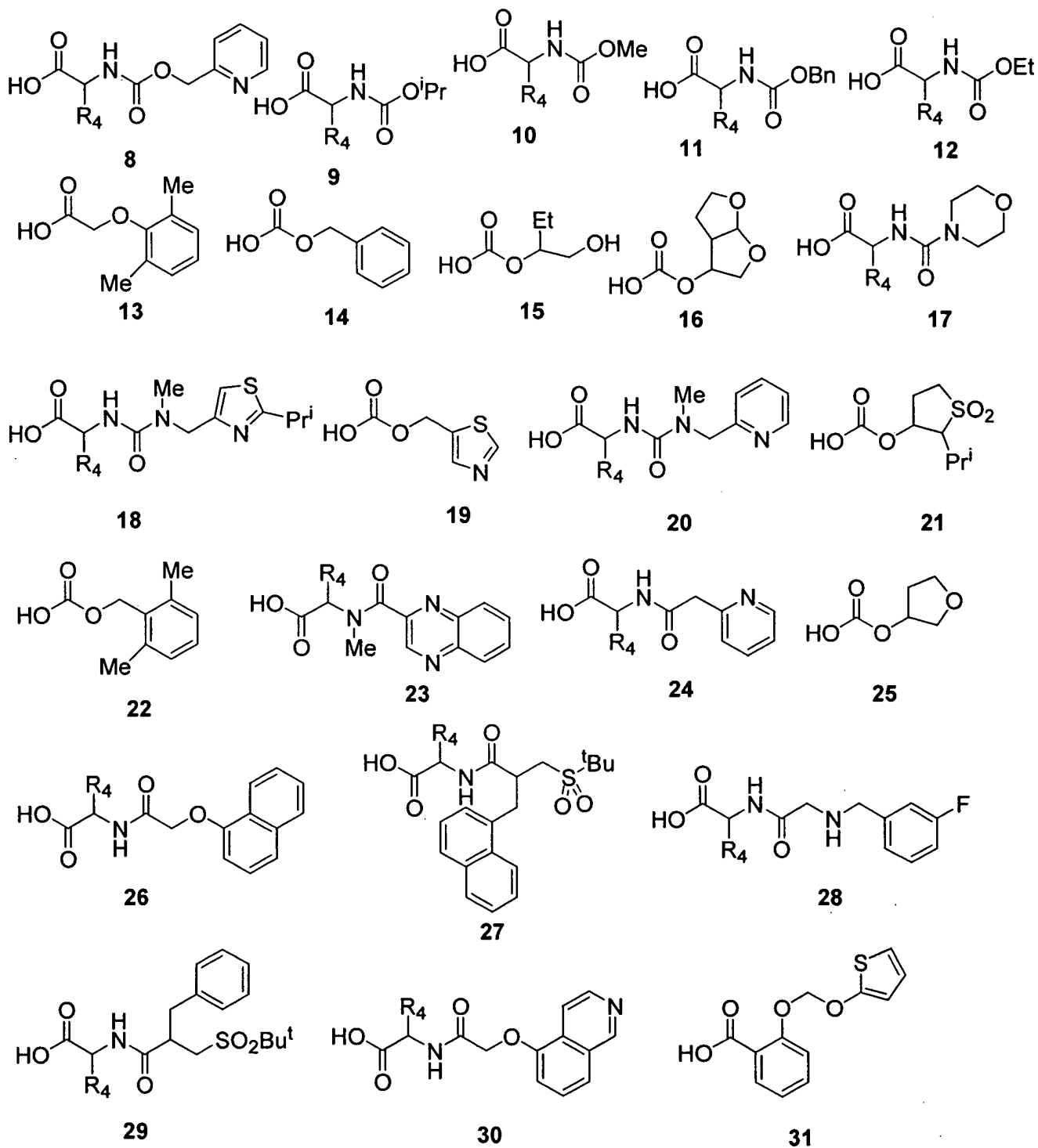
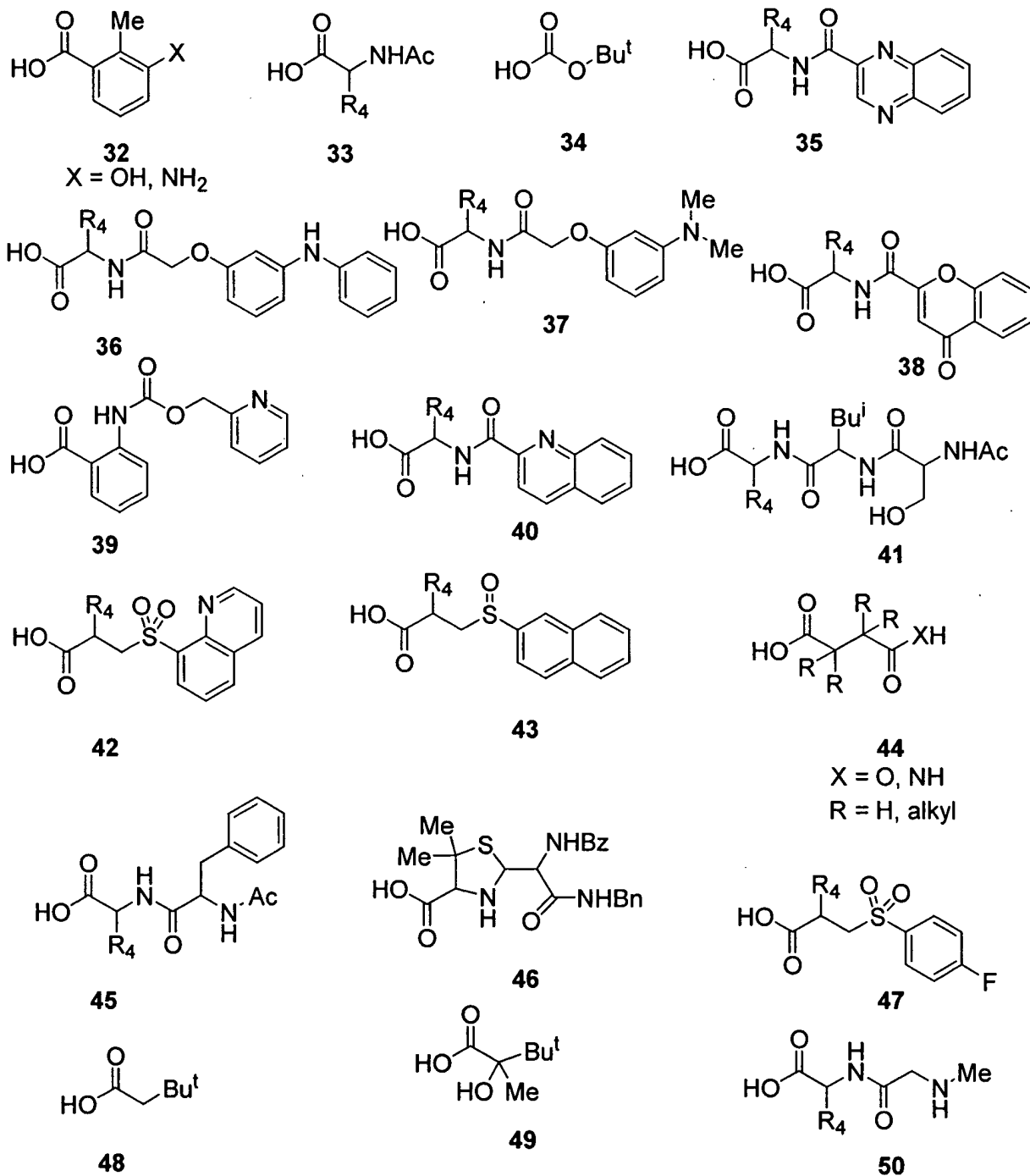


Chart 2a Structures of the R<sup>2</sup>COOH and R<sup>3</sup>COOH components



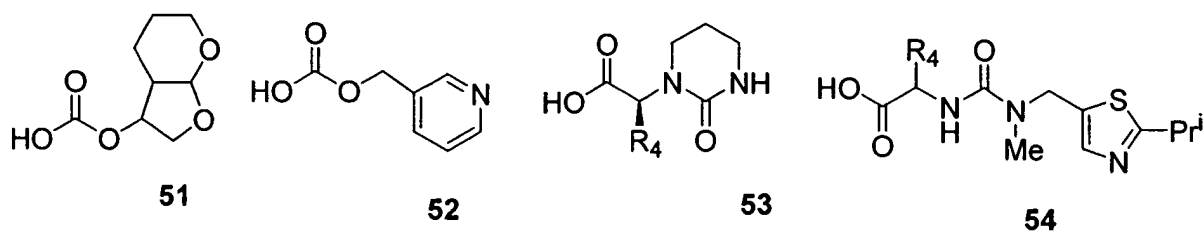
R<sup>4</sup> = alkyl, CH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CONH<sub>2</sub>, CH<sub>2</sub>SCH<sub>3</sub>, imidaz-4-ylmethyl, CH<sub>2</sub>NHAc, CH<sub>2</sub>NHCOCF<sub>3</sub>

Chart 2b Structures of the R<sup>2</sup>COOH and R<sup>3</sup>COOH components



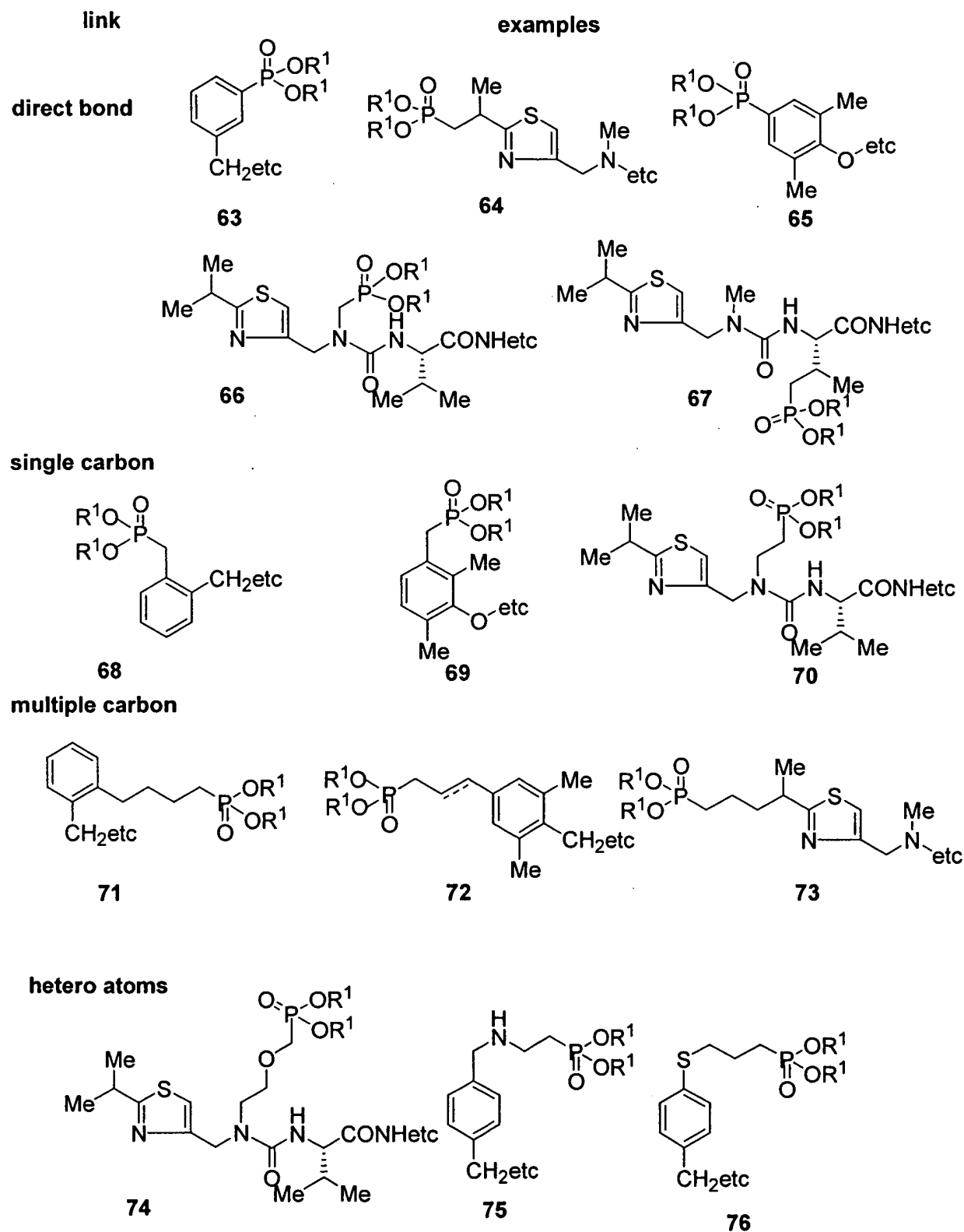
R<sup>4</sup> = alkyl, CH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CONH<sub>2</sub>, CH<sub>2</sub>SCH<sub>3</sub>, imidaz-4-ylmethyl, CH<sub>2</sub>NHAc, CH<sub>2</sub>NHCOCF<sub>3</sub>

**Chart 2c Structures of the R<sup>2</sup>COOH and R<sup>3</sup>COOH components**

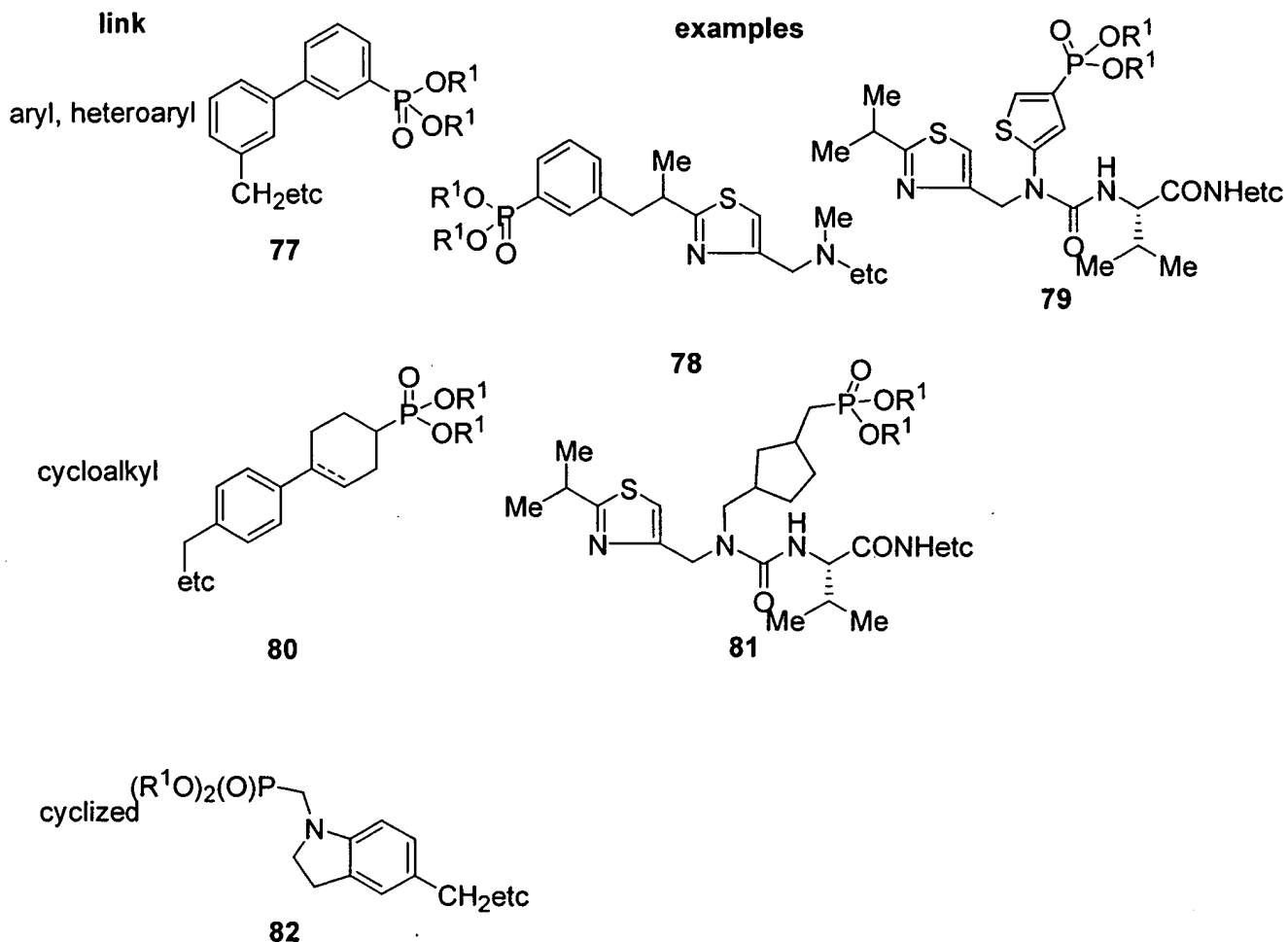


R<sup>4</sup> = alkyl, CH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CONH<sub>2</sub>, CH<sub>2</sub>SCH<sub>3</sub>, imidaz-4-ylmethyl, CH<sub>2</sub>NHAc, CH<sub>2</sub>NHCOCF<sub>3</sub>

Chart 3 Examples of the linking group between the scaffold and the phosphonate moiety.



**Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.**



## Protection of reactive substituents

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

## Preparation of the phosphonate intermediates 1

Two methods for the preparation of the phosphonate intermediate compounds **1**, in which the phosphonate moiety is attached to the isopropyl group of the carboxylic acid reactant **1.5**, are shown in Schemes 1 and 2. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme 1, 5-amino-2-dibenzylamino-1,6-diphenyl-hexan-3-ol, **1.1**, the preparation of which is described in *Org. Process Res. Dev.*, 1994, 3, 94, is reacted with a carboxylic acid  $R^2COOH$  **1.2**, or an activated derivative thereof, to produce the amide **1.3**.

The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, dimethylformamide or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, imidazolid and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid **1.2** is converted into the acid chloride, and the latter compound is reacted with an equimolar amount of the amine **1.1**, in an aprotic solvent such as, for example, tetrahydrofuran, at ambient temperature. The reaction is conducted in the presence of an organic base such as triethylamine, so as to afford the amide **1.3**.

The N, N-dibenzylamino amide product **1.3** is then transformed into the free amine compound **1.4** by means of a debenzylation procedure. The deprotection of N-benzyl amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 365. The transformation can be effected under reductive conditions, for example by the use of hydrogen or a hydrogen donor, in the presence of a

palladium catalyst, or by treatment of the N-benzyl amine with sodium in liquid ammonia, or under oxidative conditions, for example by treatment with 3-chloroperoxybenzoic acid and ferrous chloride.

Preferably, the N, N-dibenzyl compound **1.3** is converted into the amine **1.4** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75°C for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The thus-obtained amine **1.4** is then transformed into the amide **1.6** by reaction with the carboxylic acid **1.5**, or an activated derivative thereof, in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto. Preparations of the carboxylic acids **1.5** are described below, Schemes **13 - 15**. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide **1.3**.

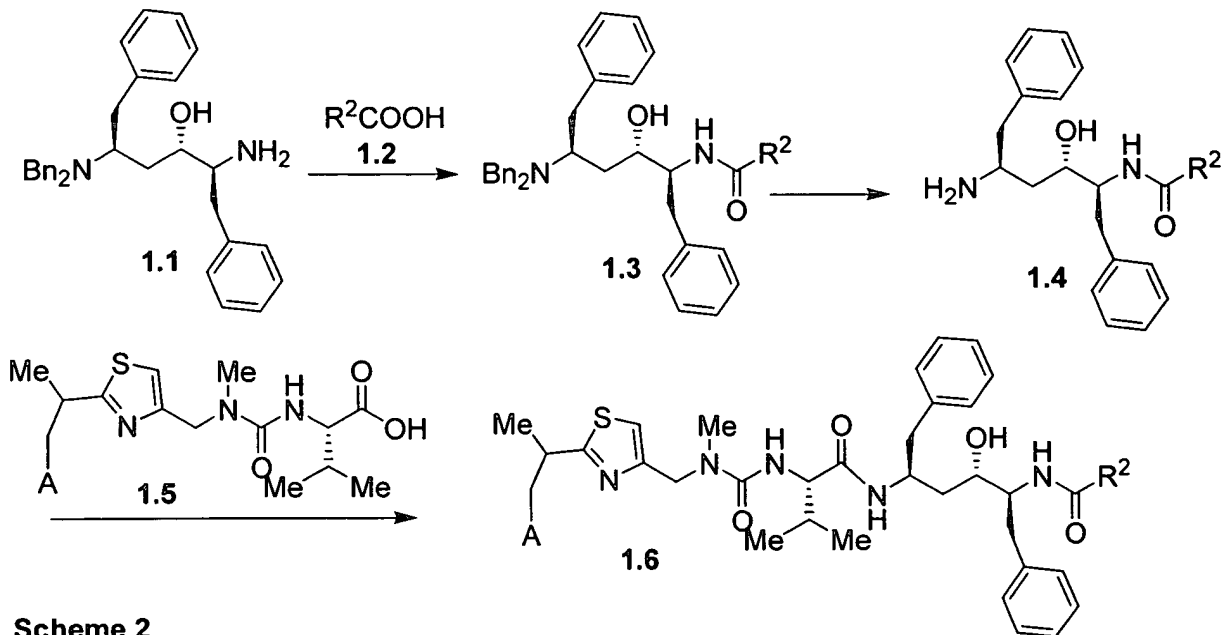
Preferably, the carboxylic acid is converted into the acid chloride, and the acid chloride is reacted with the amine **1.4** in a solvent mixture composed of an organic solvent such as ethyl acetate, and water, in the presence of a base such as sodium bicarbonate, for example as described in *Org. Process Res. Dev.*, 2000, 4, 264, to afford the amide product **1.6**.

Scheme **2** illustrates an alternative method for the preparation of the phosphonate-containing diamides **1**. In this procedure, 2-phenyl-1-[4-phenyl-2-(1-vinyl-propenyl)-[1,3,2]oxazaborinan-6-yl]-ethylamine **2.1**, the preparation of which is described in WO 9414436, is reacted with the carboxylic acid R<sup>2</sup>COOH **1.2**, or an activated derivative thereof, to afford the amide product **2.2**. The reaction is effected employing the same conditions as were described above for the preparation of the amide **1.3**. Preferably, equimolar amounts of the acid chloride derived from the carboxylic acid **1.2** is reacted with the amine **2.1** in a polar aprotic solvent such as tetrahydrofuran or dimethylformamide, at from ambient temperature to about -60°C, in the presence of an organic or inorganic base, to produce the amide **2.2**. The product is then reacted with the carboxylic acid **1.5**, or an activated derivative thereof, to afford the amide **1.6**. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide **1.3**. Preferably, the acid **1.5** and the amine **2.2** are reacted in the presence of hydroxybenztriazole, and N-ethyl-N'-dimethylaminopropyl carbodiimide, in tetrahydrofuran at ambient temperature, as described in U.S. Patent 5,484,801, to yield the amide **1.6**.

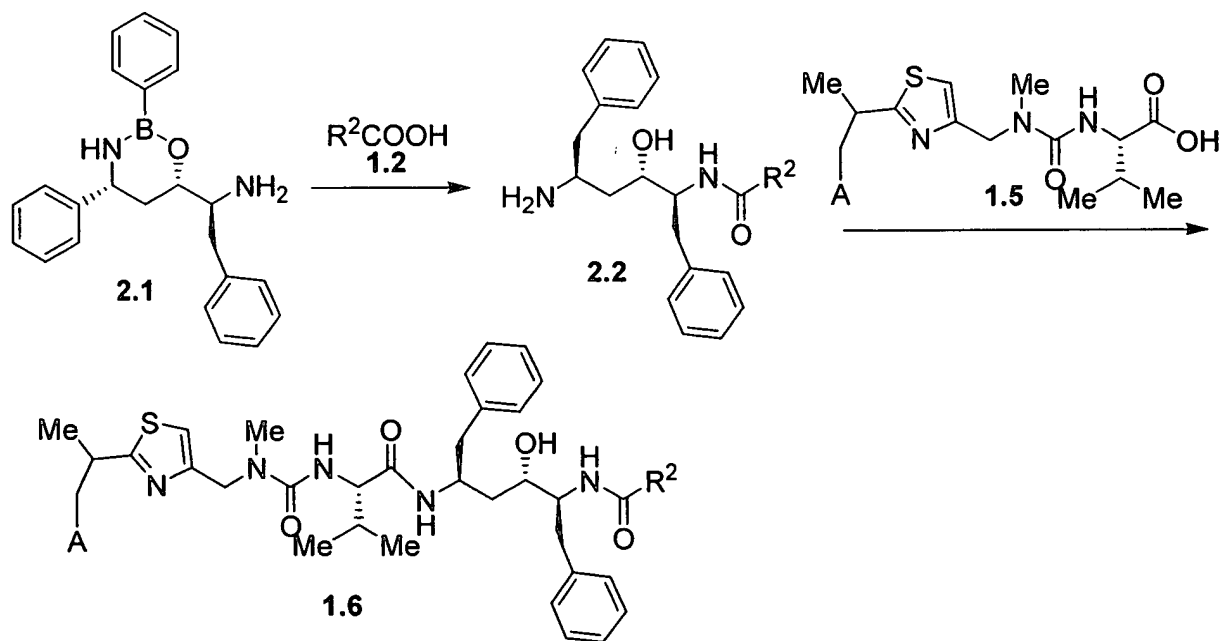
The reactions illustrated in Schemes 1 and 2 illustrate the preparation of the compounds **1.6** in which A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 3 depicts the conversion of the compounds **1.6** in which A is OH, SH, NH, as described below, into the compounds **1** in which A is the group  $\text{link-P(O)(OR}^1)_2$ . Procedures for the conversion of the group A into the group  $\text{link-P(O)(OR}^1)_2$  are described below, (Schemes **16-26**).

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below, (Scheme **27**)

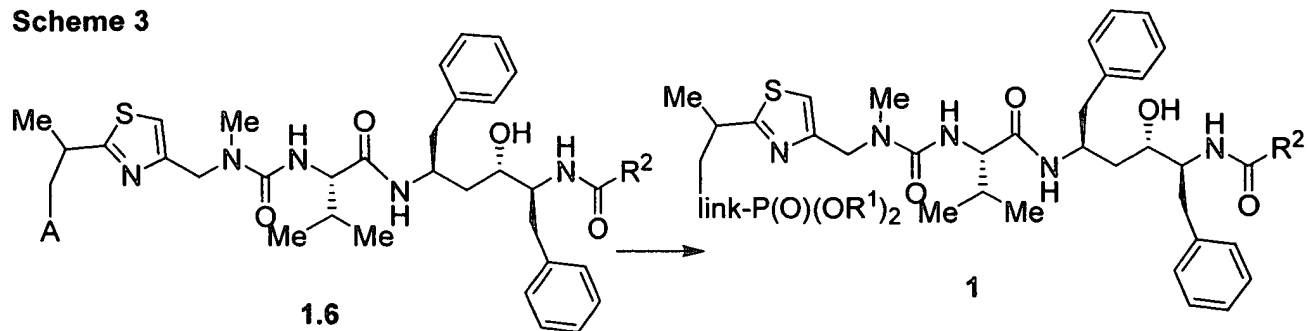
### Scheme 1



### Scheme 2



### Scheme 3



## Preparation of the phosphonate intermediates 2

Two methods for the preparation of the phosphonate intermediate compounds **2** are shown in Schemes **4** and **5**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As depicted in Scheme **4**, the tribenzylated phenylalanine derivative **4.1**, in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, as described below, is reacted with the anion **4.2** derived from acetonitrile, to afford the ketonitrile **4.3**. Preparations of the tribenzylated phenylalanine derivatives **4.1** are described below, Schemes **16-18**.

The anion of acetonitrile is prepared by the treatment of acetonitrile with a strong base, such as, for example, lithium hexamethyldisilylazide or sodium hydride, in an inert organic solvent such as tetrahydrofuran or dimethoxyethane, as described, for example, in U.S. Patent 5,491,253. The solution of the acetonitrile anion **4.2**, in an aprotic solvent such as tetrahydrofuran, dimethoxyethane and the like, is then added to a solution of the ester **4.1** at low temperature, to afford the coupled product **4.3**.

Preferably, a solution of ca. two molar equivalent of acetonitrile, prepared by the addition of ca. two molar equivalent of sodium amide to a solution of acetonitrile in tetrahydrofuran at -40°C, is added to a solution of one molar equivalent of the ester **4.1** in tetrahydrofuran at -40°C, as described in *J. Org. Chem.*, 1994, 59, 4040, to produce the ketonitrile **4.3**.

The above-described ketonitrile compound **4.3** is then reacted with an organometallic benzyl reagent **4.4**, such as a benzyl Grignard reagent or benzyllithium, to afford the ketoenamine **4.5**. The reaction is conducted in an inert aprotic organic solvent such as diethyl ether, tetrahydrofuran or the like, at from -80°C to ambient temperature.

Preferably, the ketonitrile **4.3** is reacted with three molar equivalents of benzylmagnesium chloride in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in *J. Org. Chem.*, 1994, 59, 4040, the ketoenamine **4.5**.

The ketoenamine **4.5** is then reduced, in two stages, via the ketoamine **4.6**, to produce the amino alcohol **4.7**. The transformation of the ketoenamine **4.5** to the aminoalcohol **4.7** can be effected in one step, or in two steps, with or without isolation of the intermediate ketoamine **4.6**, as described in U.S. Patent 5,491,253.

For example, the ketoenamine **4.5** is reduced with a boron-containing reducing agent such as sodium borohydride, sodium cyanoborohydride and the like, in the presence of an acid such as methanesulfonic acid, as described in *J. Org. Chem.*, 1994, 59, 4040, to afford the ketoamine **4.6**. The reaction is performed in an ethereal solvent such as, for example, tetrahydrofuran or methyl tert-butyl ether. The latter compound is then reduced with sodium borohydride-trifluoroacetic acid, as described in U.S. Patent 5,491,253, to afford the aminoalcohol **4.7**.

Alternatively, the ketoenamine **4.5** can be reduced to the aminoalcohol **4.7** without isolation of the intermediate ketoamine **4.6**. In this procedure, described in U.S. Patent 5,491,253, the ketoenamine **4.5** is reacted with sodium borohydride-methanesulfonic acid, in an ethereal solvent such as dimethoxyethane and the like. The reaction mixture is then treated with a quenching agent such as triethanolamine, and the procedure is continued by the addition of sodium borohydride and a solvent such as dimethyl formamide or dimethylacetamide or the like, to afford the aminoalcohol **4.7**.

The aminoalcohol **4.7** is converted into the amide **4.9** by reaction with the acid  $R^3COOH$  **4.8**, or an activated derivative thereof, to produce the amide **4.9**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

The dibenzylated amide product **4.9** is deprotected to afford the free amine **4.10**. The conditions for the debenzylation reaction are the same as those described above for the deprotection of the dibenzyl amine **1.3** to yield the amine **1.4**, (Scheme 1).

The amine **4.10** is then reacted with the carboxylic acid  $R^2COOH$  **1.2**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

Alternatively, the amide **4.11** can be prepared by means of the sequence of reactions illustrated in Scheme 5.

In this sequence, the tribenzylated amino acid derivative **4.1** is converted, by means of the reaction sequence shown in Scheme 4 into the dibenzylated amine **4.7**. This compound is then converted into a protected derivative, for example the tert-butoxycarbonyl (BOC) derivative **5.1**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine can be reacted with di-tert-butoxycarbonylanhydride (BOC

anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like.

Preferably, the amine is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in U.S. Patent 5,914,3332, to yield the BOC-protected product **5.1**.

The N-benzyl protecting groups are then removed from the amide product **5.1** to afford the free amine **5.2**. The conditions for this transformation are similar to those described above for the preparation of the amine **1.4**, (Scheme 1).

Preferably, the N, N-dibenzyl compound **5.1** is converted into the amine **5.2** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75°C for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The amine compound **5.2** is then reacted with the carboxylic acid  $R^2COOH$  **1.2**, or an activated derivative thereof, to produce the amide **5.3**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**, to afford the amide product **5.3**.

The latter compound is then converted into the amine **5.4** by removal of the BOC protecting group. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

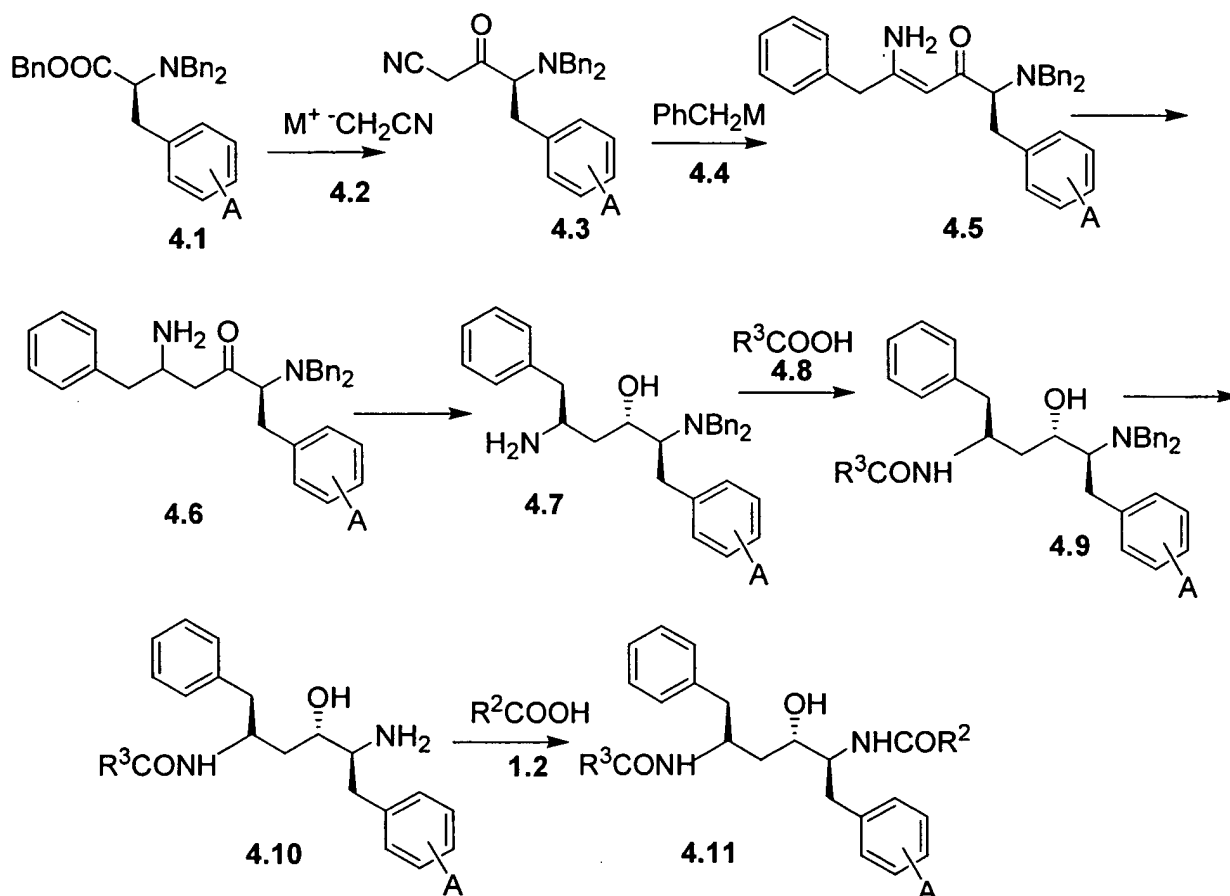
Preferably, the BOC group is removed by treatment of the substrate **5.3** with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in U.S. Patent 5,914,232, to afford the free amine product **5.4**.

The free amine thus obtained is then reacted with the carboxylic acid  $R^3COOH$  **4.8**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

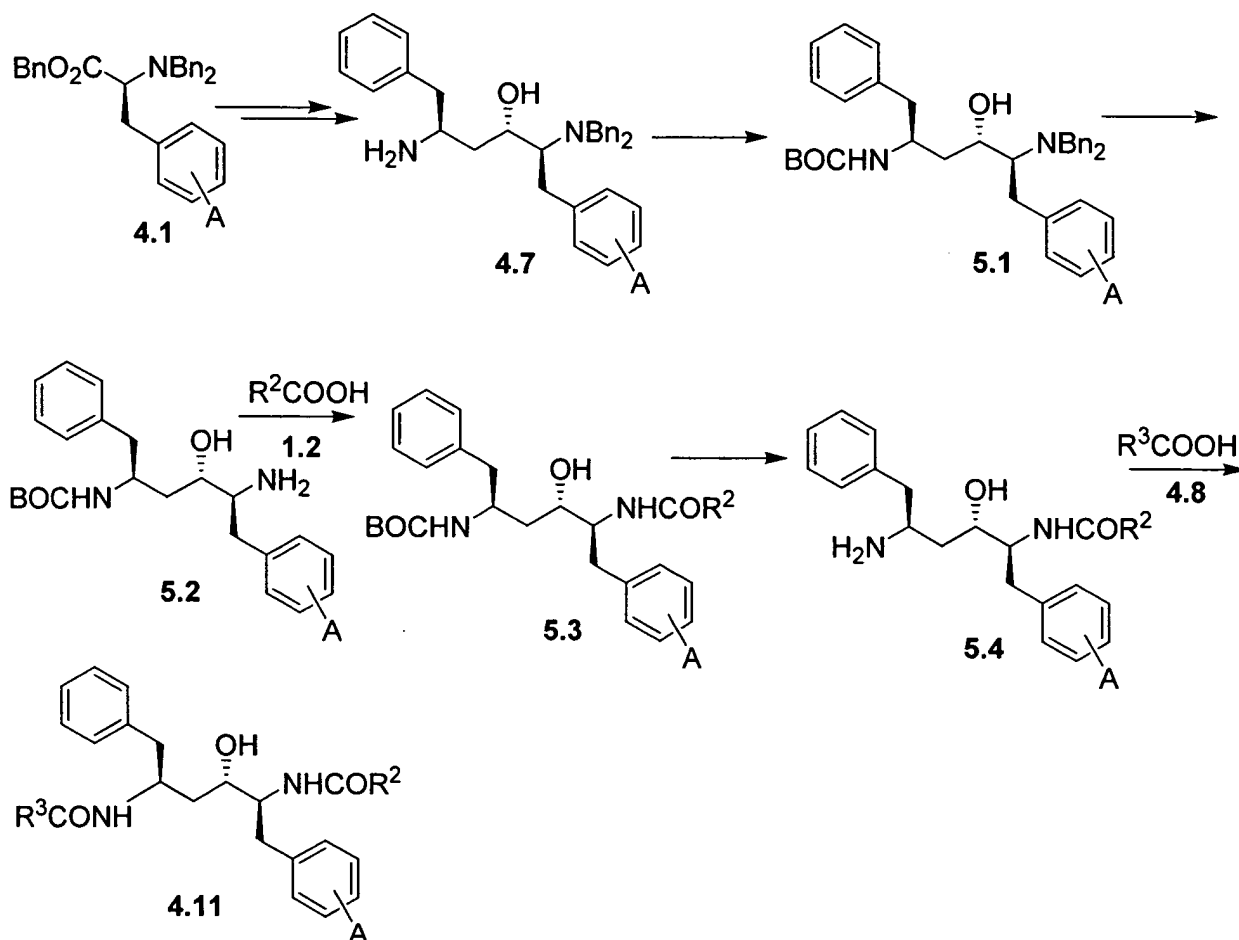
The reactions shown in Schemes 4 and 5 illustrate the preparation of the compounds **4.11** in which A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 6 depicts the conversion of the

compounds **4.11** in which A is OH, SH, NH, as described below, into the compounds **2**. Procedures for the conversion of the group A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> are described below, (Schemes 16-26).

**Scheme 4**



**Scheme 5**



### Preparation of the phosphonate intermediates 3

The phosphonate ester intermediate compounds **3** can be prepared by two alternative methods, illustrated in Schemes 7 and 8. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme 7, 4-dibenzylamino-3-oxo-5-phenyl-pentanenitrile **7.1**, the preparation of which is described in *J. Org. Chem.*, 1994, 59, 4040, is reacted with a substituted benzylmagnesium halide reagent **7.2**, in which the group B is a substituent, protected if appropriate, which can be converted, during or after the sequence of reactions shown in Scheme 7, into the moiety link-P(O)(OR<sup>1</sup>)<sub>2</sub>. Examples of the substituent B are Br, [OH], [SH], [NH<sub>2</sub>] and the like; procedures for the transformation of these groups into the phosphonate moiety are shown below in Schemes 16-26. The conditions for the reaction between the benzylmagnesium

halide and the ketonitrile are similar to those described above for the preparation of the ketoenamine **4.5** (Scheme 4).

Preferably, the ketonitrile **7.1** is reacted with three molar equivalents of the substituted benzylmagnesium chloride **7.2** in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in *J. Org. Chem.*, 1994, 59, 4040, the ketoenamine **7.3**.

The thus-obtained ketoenamine **7.3** is then transformed, via the intermediate compounds **7.4**, **7.5**, **7.6**, and **7.7** into the diacylated carbinol **7.8**. The conditions for each step in the conversion of the ketoenamine **7.3** to the diacylated carbinol **7.8** are the same as those described above (Scheme 4) for the transformation of the ketoenamine **4.5** into the diacylated carbinol **4.11**.

The diacylated carbinol **7.8** is then converted into the phosphonate ester **3**, using procedures illustrated below in Schemes 16-26.

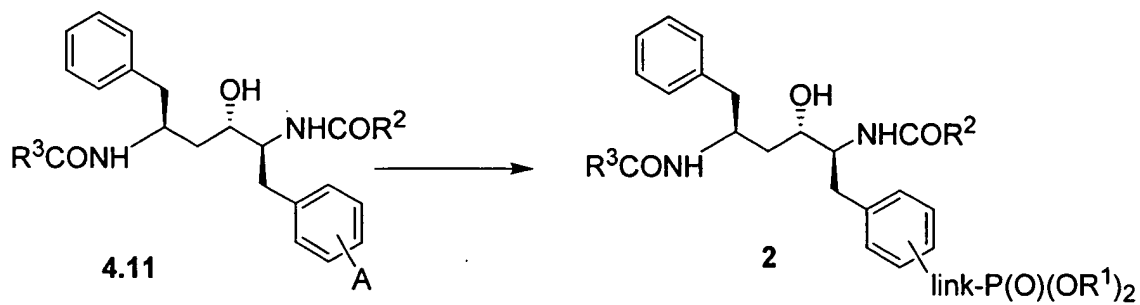
Alternatively, the phosphonate esters **3** can be obtained by means of the reactions illustrated in Scheme 8. In this procedure, the amine **7.5**, the preparation of which is described above, (Scheme 7) is converted into the BOC derivative **8.1**. The conditions for the introduction of the BOC group are similar to those described above for the protection of the amine **5.1**, (Scheme 5).

Preferably, the amine is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in U.S. Patent 5,914,332, to yield the BOC-protected product **8.1**.

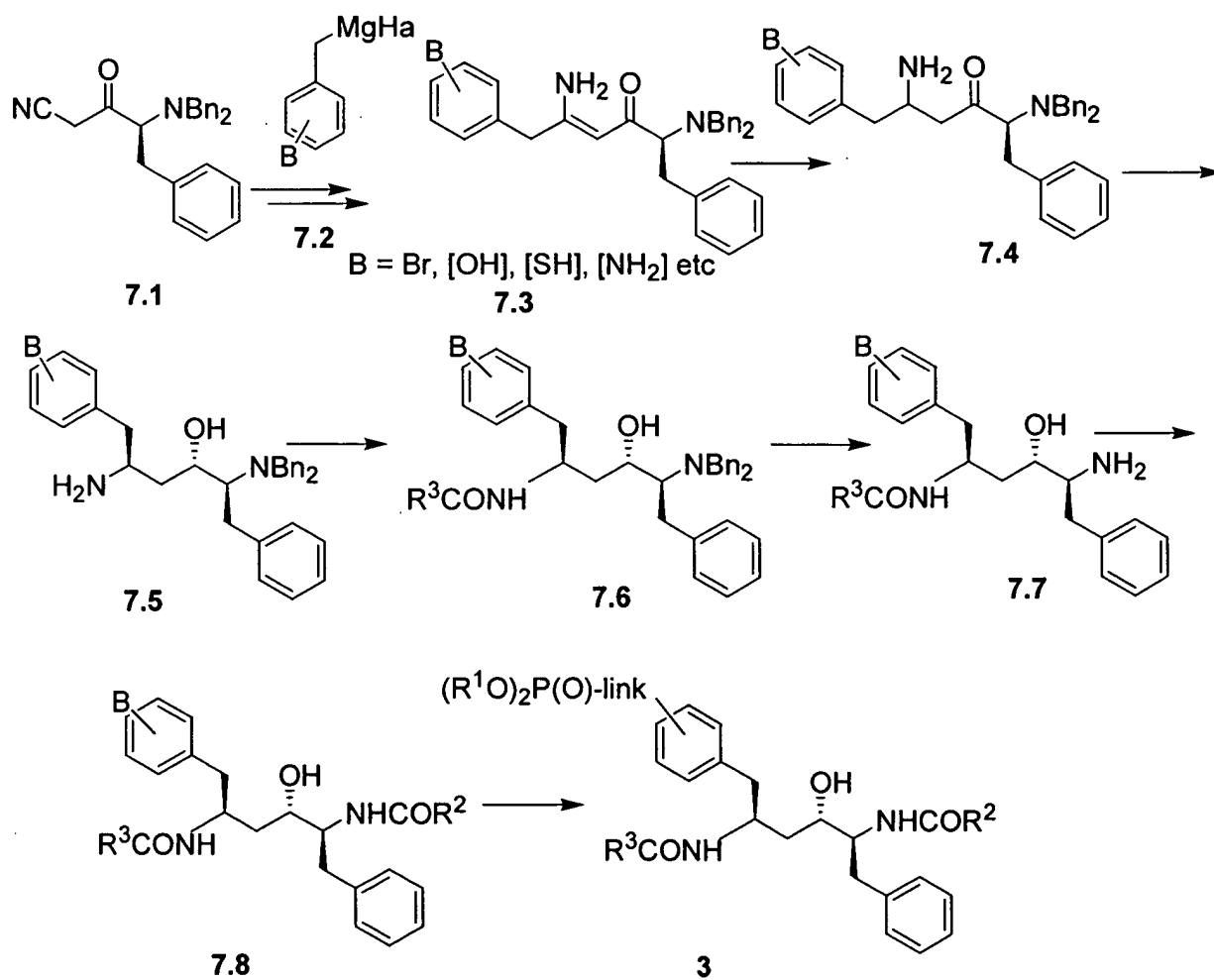
The BOC-protected amine **8.1** is then converted, via the intermediates **8.2**, **8.3** and **8.4** into the diacylated carbinol **8.5**. The reaction conditions for this sequence of reactions are similar to those described above for the transformation of the BOC-protected amine **5.1** into the diacylated carbinol **5.4** (Scheme 5).

The diacylated carbinol **8.5** is then converted into the phosphonate ester **3**, using procedures illustrated below in Schemes 16-26.

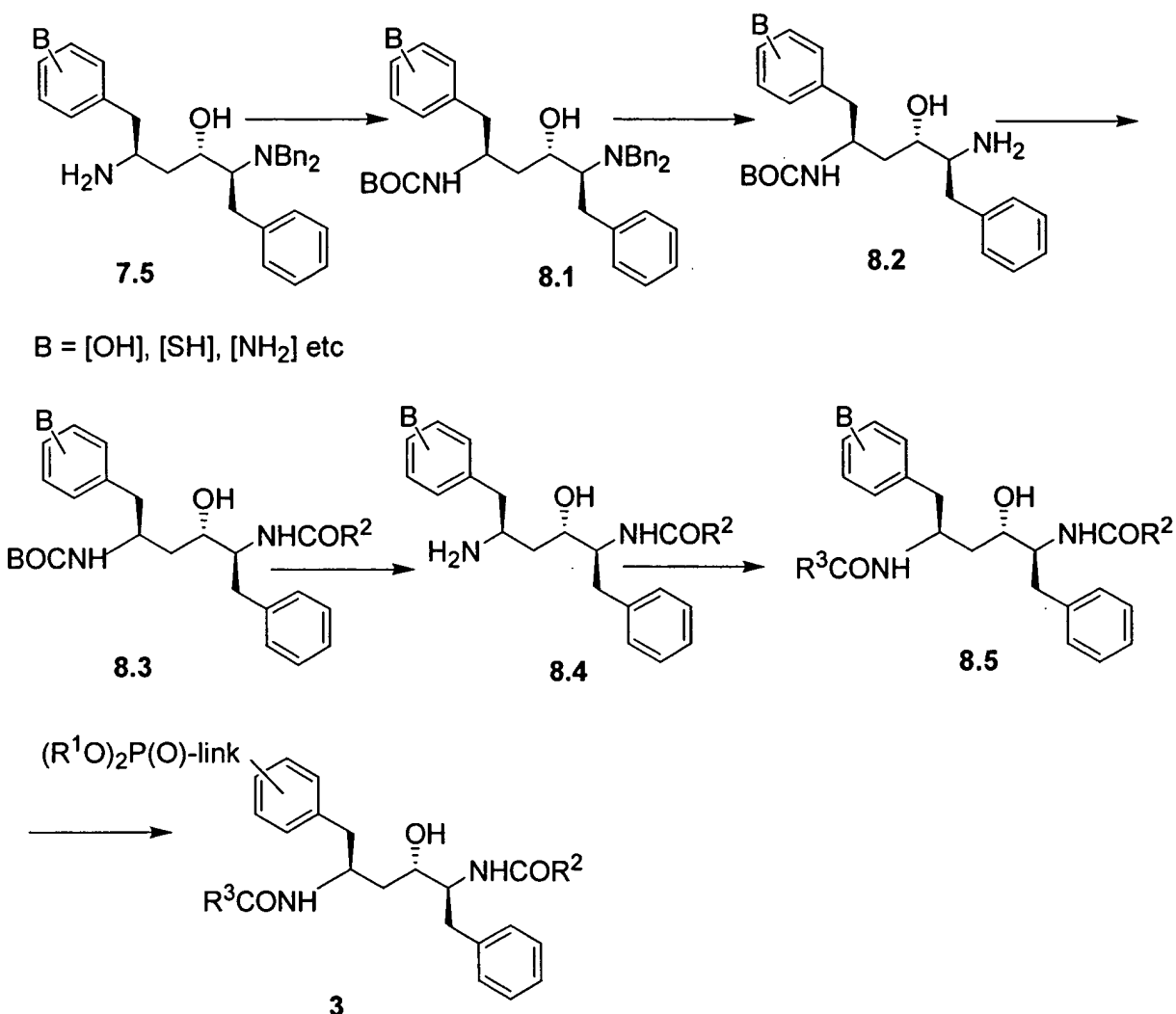
**Scheme 6**



**Scheme 7**



**Scheme 8**

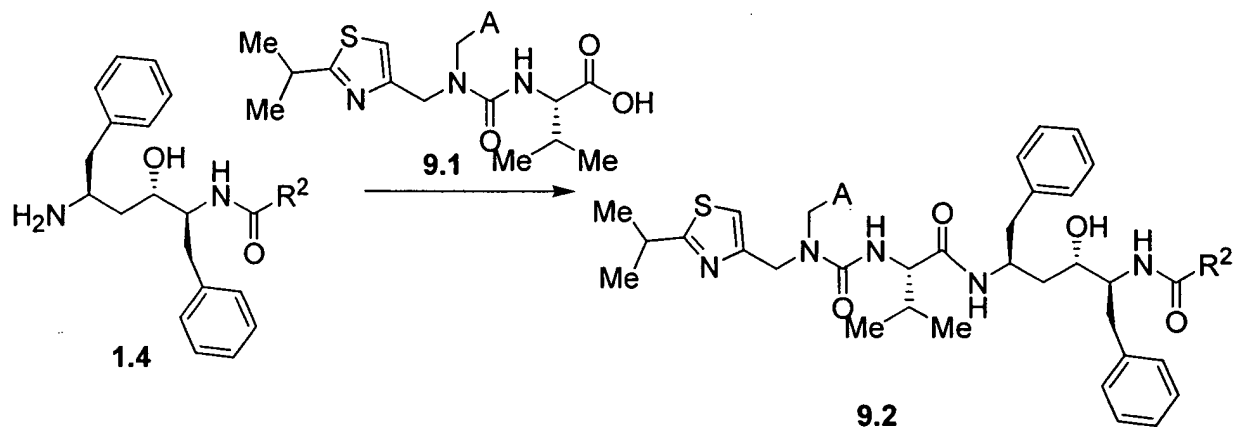


#### Preparation of the phosphonate intermediates 4

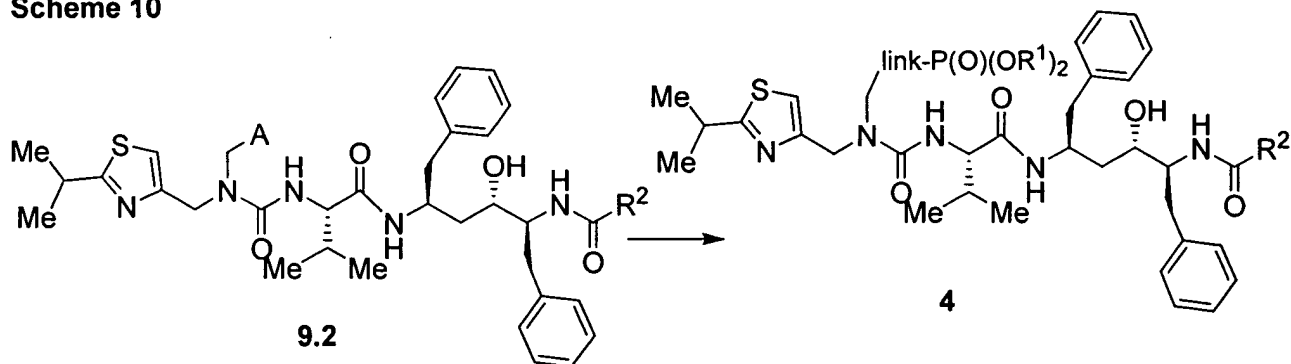
Scheme 9 illustrates the preparation of the intermediate phosphonate esters 9.2 in which the substituent A, which is the phosphonate ester moiety or a precursor group thereto, is attached to one of the urea nitrogen atoms in the carboxylic acid reactant 9.1. The preparation of the carboxylic acid reactant 9.1 is described below, Schemes 24-25. In this procedure, the amine 1.4, prepared as described in Scheme 1, is reacted with the carboxylic acid 9.1, to afford the amide 9.2. The reaction between the amine 1.4 and the carboxylic acid 9.1, or an activated derivative thereof, is conducted under the same general conditions as those described above for the preparation of the amide 1.6 (Scheme 1). Preferably, the reactants are combined in the presence of hydroxybenztriazole and a carbodiimide, as described in U.S. Patent 5,484,801, to yield the amide product 9.2.

The procedure shown in Scheme 9 describes the preparation of the compounds 9.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor group thereto, such as [OH], [SH], [NH], as described below. Scheme 10 depicts the conversion of compounds 9.2 in which A is [OH], [SH], [NH], into the compounds 4, in which the group A has been transformed into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>. The methods for accomplishing this transformation are described below, Schemes 16-26.

#### Scheme 9



#### Scheme 10



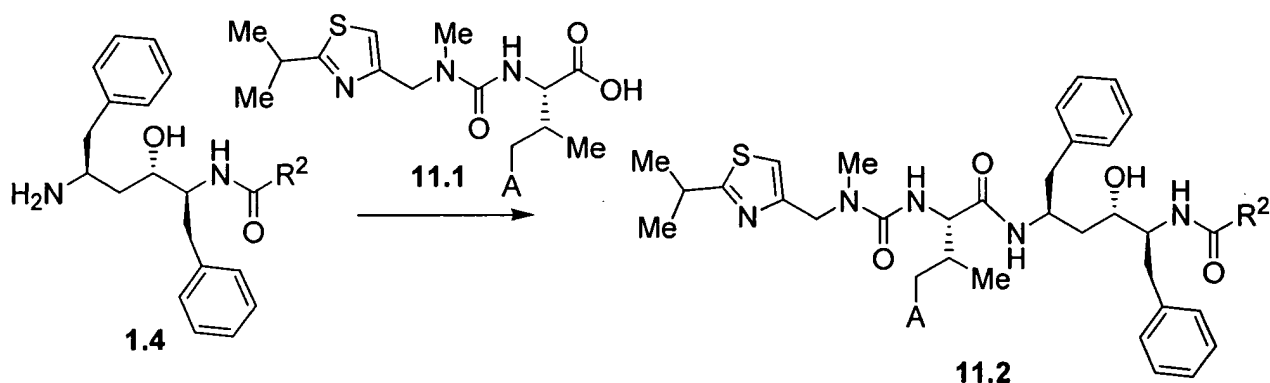
#### Preparation of the phosphonate intermediates 5

Scheme 11 illustrates the preparation of the intermediate phosphonate esters 11.2 in which the substituent A, which is the phosphonate ester moiety or a precursor group thereto, is attached to the valine moiety in the carboxylic acid reactant 11.1. The preparation of the carboxylic acid reactant 11.1 is described below, Scheme 26. The reaction between the amine 1.4 and the carboxylic acid 11.1, or an activated derivative thereof, is conducted under the same general conditions as those described above for the preparation of the amide 1.3 (Scheme 1).

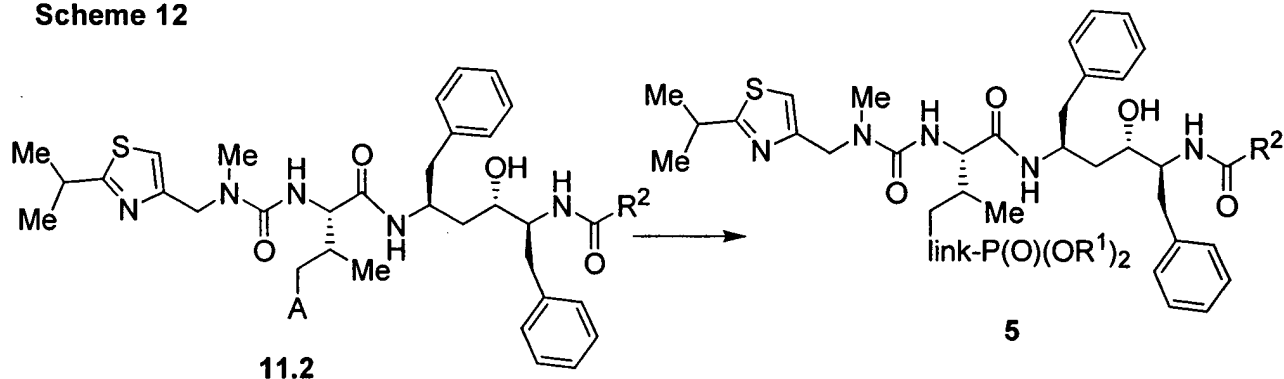
Preferably, the reactants are combined in the presence of hydroxybenztriazole and a carbodiimide, as described in U.S. Patent 5,484,801, to yield the amide product **11.2**.

The procedure shown in Scheme 11 describes the preparation of the compounds **11.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor group thereto, such as [OH], [SH, [NH] Ha, as described below. Scheme 12 depicts the conversion of compounds **11.2** in which A is [OH], [SH, [NH] Br, into the compounds **5**, in which the group A has been transformed into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>. The methods for accomplishing this transformation are described below, Schemes 16-26.

**Scheme 11**



**Scheme 12**



#### **Preparation of carboxylic acids 1.5, with a phosphonate moiety attached to the isopropyl group**

Scheme 13 illustrates the preparation of carboxylic acid reactants **1.5**, in which a substituent A, attached to the isopropyl group, is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor group thereto, such as [OH], [SH, [NH] Br. During the series of reaction shown in Scheme 13, the group A may, at an appropriate stage, be converted into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>,

according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **1.5**, in which A is link-P(O)(OR<sup>1</sup>)<sub>2</sub>, may be incorporated into the diamide compounds **1.6**, as described above, (Schemes **1** and **2**) before effecting the transformation of the group A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>.

As shown in Scheme **13**, a substituted derivative of isobutyramide **13.1** is converted into the corresponding thioamide **13.2**. The conversion of amides into thioamides is described in Synthetic Organic Chemistry, by R. B. Wagner and H. D. Zook, Wiley, 1953, p. 827. The amide is reacted with a sulfur-containing reagent such as phosphorus pentasulfide or Lawesson's reagent, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Wiley, Vol. 13, p. 38, to yield the thioamide **13.2**. Preferably, the amide **13.1** is reacted with phosphorus pentasulfide in ether solution, at ambient temperature, as described in U.S. Patent 5,484,801, to afford the amide **13.2**. The latter compound is then reacted with 1,3-dichloroacetone **13.3** to produce the substituted thiazole **13.4**. The preparation of thiazoles by the reaction between a thioamide and a chloroketone is described, for example, in Heterocyclic Chemistry, by T. A. Gilchrist, Longman, 1997, p. 321. Preferably, equimolar amounts of the reactants are combined in acetone solution at reflux temperature, in the presence of magnesium sulfate, as described in U.S. Patent 5,484,801, to produce the thiazole product **13.4**. The chloromethyl thiazole **13.4** is then reacted with methylamine to afford the substituted methylamine **13.6**. The preparation of amines by the reaction of amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Typically, the components are reacted together in a polar solvent such as an alkanol or dimethylformamide and the like. Preferably, the chloro compound **13.4** is reacted with excess aqueous methylamine at ambient temperature, as described in U.S. Patent 5,484,801, to afford the amine product **13.6**. The amine is then converted into the urea derivative **13.8** by reaction with an activated derivative of the valine carbamic acid **13.7**, in which X is a leaving group such as alkanoyloxy or 4-nitrophenoxy. The preparation of ureas by the reaction between carbamic acid derivatives and amines is described in *Chem. Rev.*, 57, 47, 1957. Suitable carbamic acid derivatives are prepared by the reaction between an amine and an alkyl or aryl chloroformate, for example as described in WO 9312326. Preferably, the reaction is performed using carbamic acid derivative **13.7**, in which X is 4-nitrophenoxy, and the amine **13.8**; the reaction is conducted at about 0°C in an inert solvent such as dichloromethane, in the presence of

an organic base such as dimethylaminopyridine or N-methylmorpholine, as described in U.S. Patent 5,484,801, to yield the urea product **13.8**. The ester group present in the urea product **13.8** is then hydrolyzed to afford the corresponding carboxylic acid **1.5**. Hydrolysis methods for converting esters into carboxylic acids are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 981. The methods include the use of enzymes such as pig liver esterase, and chemical methods such as the use of alkali metal hydroxides in aqueous organic solvent mixtures. Preferably, the methyl ester is hydrolyzed by treatment with lithium hydroxide in aqueous dioxan, as described in U.S. Patent 5,848,801, to yield the carboxylic acid **1.5**.

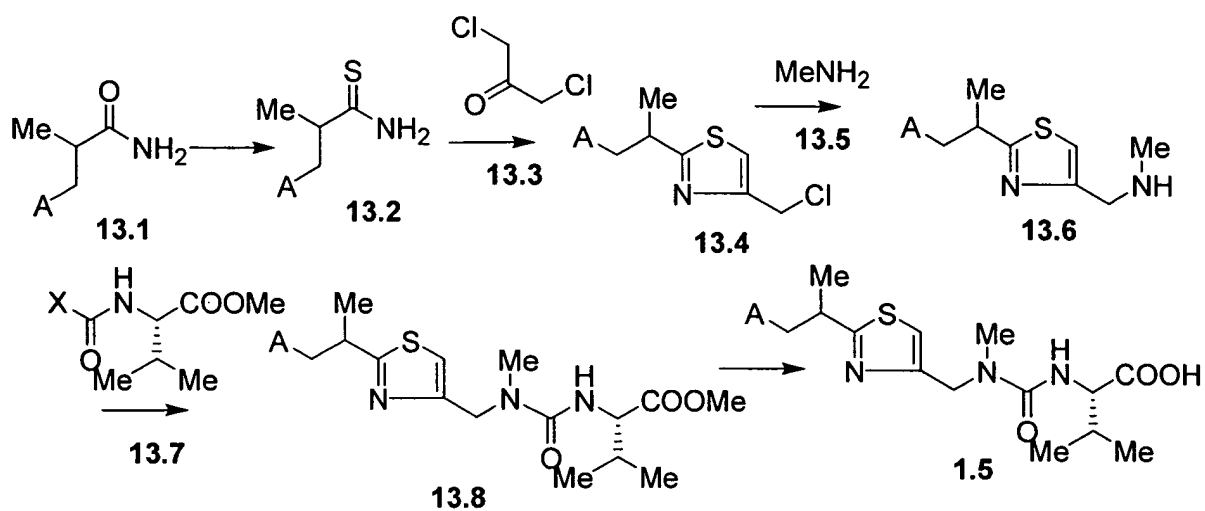
Scheme **14** illustrates the preparation of the carboxylic acids **9.1** in which the group A, attached to the amine moiety, is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor group thereto, such as [OH], [SH], [NH] Br. During the series of reaction shown in Scheme **14**, the group A may, at an appropriate stage, be converted into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **9.1**, in which A is link-P(O)(OR<sup>1</sup>)<sub>2</sub>, may be incorporated into the diamide compounds **9.2**, as described above, (Scheme **9**) before effecting the transformation of the group A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>.

As shown in Scheme **14**, 4-chloromethyl-2-isopropyl-thiazole **14.1**, prepared as described in WO 9414436, is reacted with an amine **14.2**, in which A is as described above, to afford the amine **13.6**. The conditions for the alkylation reaction are the same as those described above for the preparation of the amine **13.6**. The product is then transformed, via the intermediate ester **14.4**, into the carboxylic acid **9.1**. The conditions for the reactions required to transform the amine **14.3** into the carboxylic acid **9.1** are the same as those described above (Scheme **13**) for the analogous chemical steps.

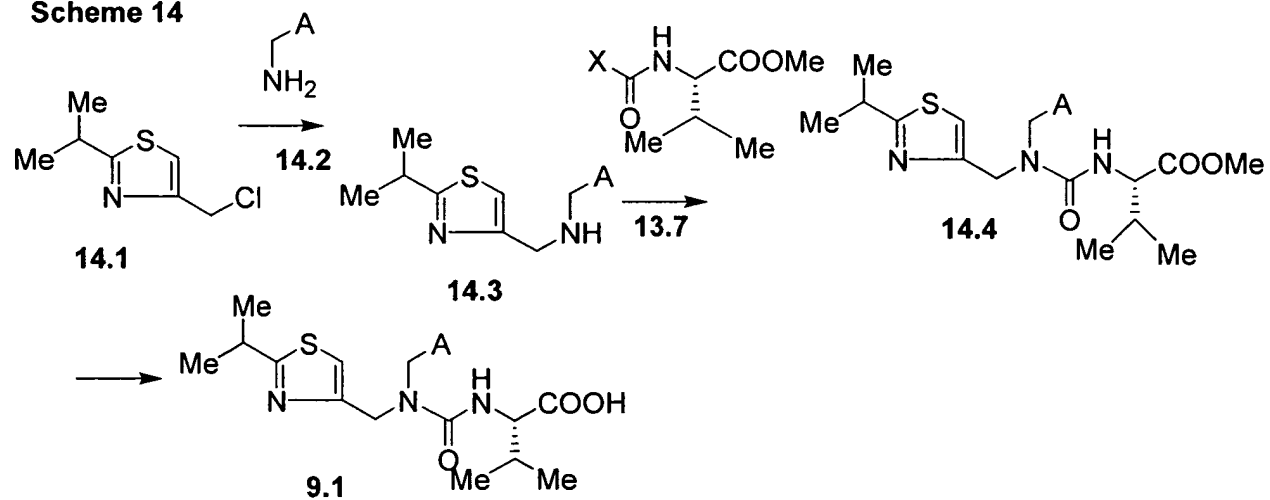
Scheme **15** illustrates the preparation of the carboxylic acids **11.1** in which the group A, attached to the valine moiety, is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor group thereto, such as [OH], [SH], [NH] Br. During the series of reaction shown in Scheme **15**, the group A may, at an appropriate stage, be converted into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **11.1**, in which A is link-P(O)(OR<sup>1</sup>)<sub>2</sub> may be incorporated into the diamide compounds **11.2**, as described above, (Scheme **11**) before effecting the transformation of the group A into the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>.

As shown in Scheme 15, (2-isopropyl-thiazol-4-ylmethyl)-methyl-amine, **15.1**, prepared as described in WO 9414436, is reacted with a substituted valine derivative **15.2**, in which the group A is as defined above. Methods for the preparation of the valine derivatives **15.2** are described below, Scheme 26. The resultant ester **15.3** is then hydrolyzed, as described above, to afford the carboxylic acid **11.1**

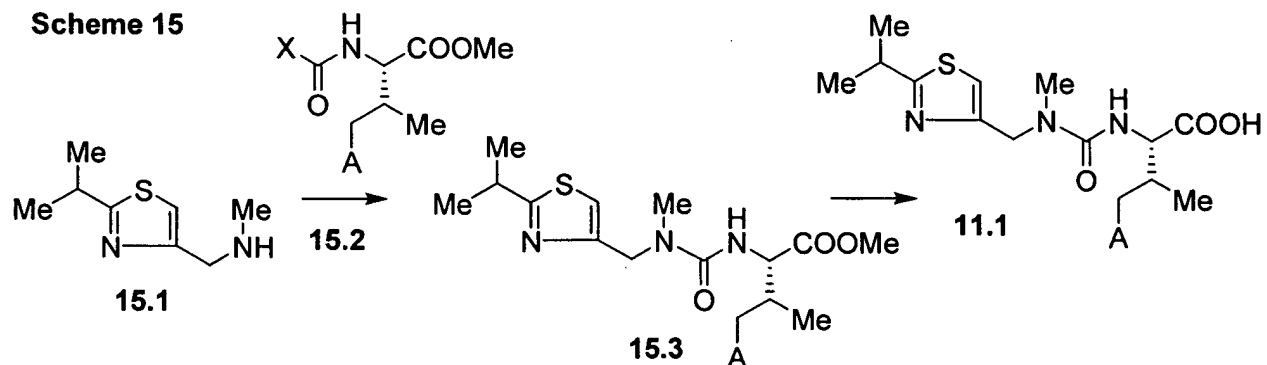
**Scheme 13**



**Scheme 14**



**Scheme 15**



#### Preparation of phenylalanine derivatives 4.1 incorporating phosphonate moieties

Scheme 16 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 16.1.

In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester 16.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 16.2 is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Thiophenols may also be protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester 16.3 is then reacted with a benzyl or substituted benzyl halide and a base, for example as described in U.S. Patent 5,491,253, to afford the N, N-dibenzyl product 16.4. For example, the amine 16.3 is reacted at ca. 90°C with two molar equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, to afford the tribenzylated product 16.4, as described in U.S. Patent 5,491,253. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient temperature, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972. S-Adamantyl groups can be removed by treatment with mercuric trifluoroacetate in acetic acid, as described in *Chem. Pharm. Bull.*, 26, 1576, 1978.

The resultant phenol or thiophenol **16.5** is then reacted under various conditions to provide protected phenylalanine derivatives **16.9**, **16.10** or **16.11**, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **16.5** is reacted with a dialkyl bromoalkyl phosphonate **16.6** to afford the product **16.9**. The alkylation reaction between **16.5** and **16.6** is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **16.9**.

For example, as illustrated in Scheme 16, Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, **16.12** is converted, as described above, into the benzyl ester **16.13**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972, to afford the silyl ether **16.14**. This compound is then converted, as described above, into the tribenzylated derivative **16.15**. The silyl protecting group is removed by treatment of **16.15** with a tetrahydrofuran solution of tetrabutyl ammonium fluoride at ambient temperature, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972, to afford the phenol **16.16**. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **16.17** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **16.18**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **16.12**, different hydroxy or thio-substituted phenylalanine derivatives **16.1**, and/or different bromoalkyl phosphonates **16.6**, the corresponding ether or thioether products **16.9** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **16.5** is reacted with a dialkyl hydroxymethyl phosphonate **16.7** under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds **16.10**. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for

example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **16.10**.

For example, as shown in Scheme 16, Example 2, 3-mercaptophenylalanine **16.19**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **16.20**. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in *Bull. Chem. Soc. Jpn.*, 37, 433, 1974, to afford the 4-methoxybenzyl thioether **16.21**. This compound is then converted, as described above for the preparation of the compound **16.4**, into the tribenzyl derivative **16.22**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **16.22** with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in *J. Org. Chem.*, 52, 4420, 1987, to afford the thiol **16.23**. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with diethyl hydroxymethyl phosphonate **16.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in *Synthesis*, 4, 327, 1998, to yield the thioether product **16.24**.

Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **16.19**, different hydroxy or mercapto-substituted phenylalanines **16.1**, and/or different dialkylhydroxymethyl phosphonates **16.7**, the corresponding products **16.10** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **16.5** is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **16.8** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **16.11**.

For example, as illustrated in Scheme 16, Example 3, 3-hydroxyphenylalanine **16.25** (Fluka) is converted, using the procedures described above, into the tribenzylated compound **16.26**. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **16.27**, prepared as described in *Tetrahedron Lett.*, 1986, 27, 1477, to afford the ether product **16.28**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **16.25**, different hydroxy or mercapto-substituted phenylalanines **16.1**,

and/or different dialkyl trifluoromethanesulfonyloxymethylphosphonates **16.8**, the corresponding products **16.11** are obtained.

Scheme 17 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted tribenzylated phenylalanine derivative **17.3** and a dialkyl aminoalkylphosphonate **17.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **17.1** is converted into the tribenzylated derivative **17.2** by reaction with three equivalents of a benzyl halide, for example, benzyl chloride, in the presence of an organic or inorganic base such as diazabicyclononene or potassium carbonate. The reaction is conducted in a polar solvent optionally in the additional presence of water. For example, the aminoacid **17.1** is reacted with three equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, as described in U.S. Patent 5,491,253, to afford the product **17.2**. The latter compound is then oxidized to afford the corresponding aldehyde **17.3**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **17.3**. For example, the carbinol **17.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in *J. Org. Chem.*, 43, 2480, 1978, to yield the aldehyde **17.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **17.4** in the presence of a suitable reducing agent to afford the amine product **17.5**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990.

For example, 3-(hydroxymethyl)-phenylalanine **17.6**, prepared as described in *Acta Chem. Scand. Ser. B*, 1977, B31, 109, is converted, as described above, into the formylated

derivative **17.7**. This compound is then reacted with a dialkyl aminoethylphosphonate **17.8**, prepared as described in *J. Org. Chem.*, 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **17.9**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **17.6**, different hydroxymethyl phenylalanines **17.1**, and/or different aminoalkyl phosphonates **17.4**, the corresponding products **17.5** are obtained.

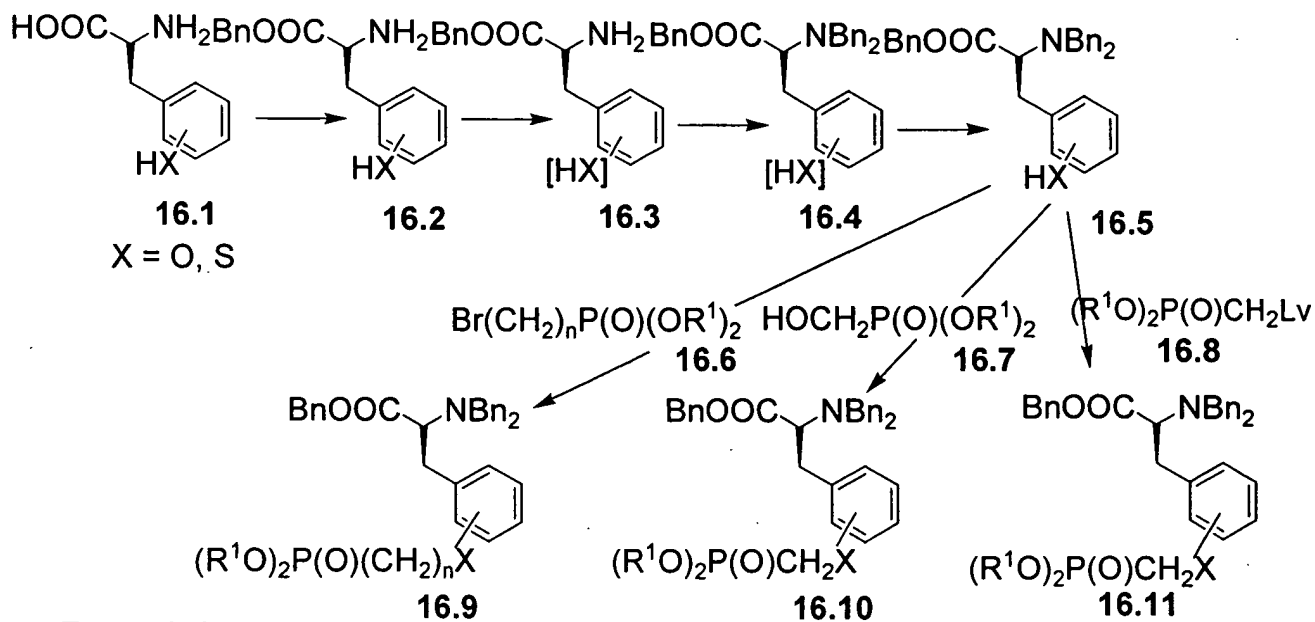
Scheme **18** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **18.1** is converted, as described above, (Scheme **17**) into the tribenzylated derivative **18.2**. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **18.3** to produce the phosphonate ester **18.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992.

For example, 3-bromophenylalanine **18.5**, prepared as described in *Pept. Res.*, 1990, 3, 176, is converted, as described above, (Scheme **17**) into the tribenzylated compound **18.6**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **18.7**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the phosphonate product **18.8**.

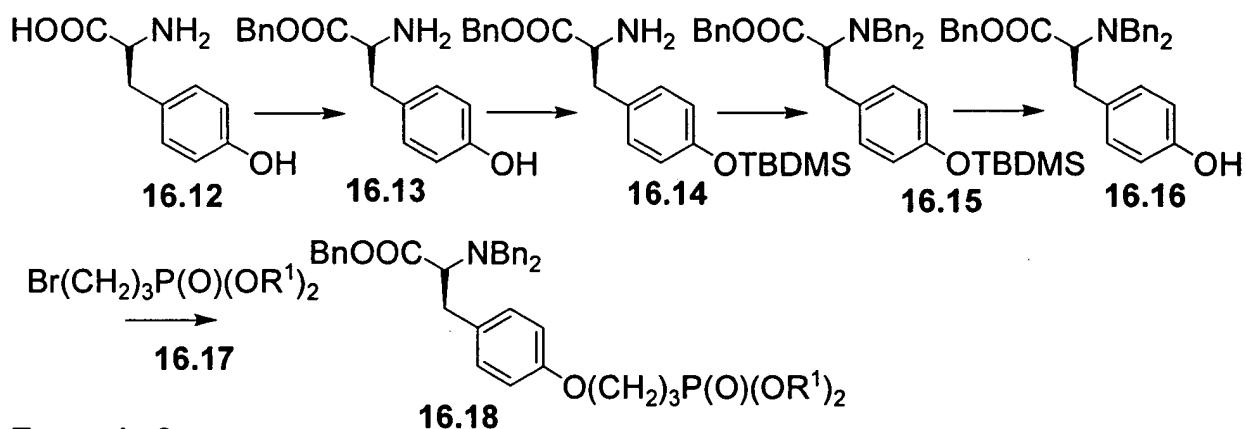
Using the above procedures, but employing, in place of 3-bromophenylalanine **18.5**, different bromophenylalanines **18.1**, and/or different dialkylphosphites **18.3**, the corresponding products **18.4** are obtained.

# Scheme 16

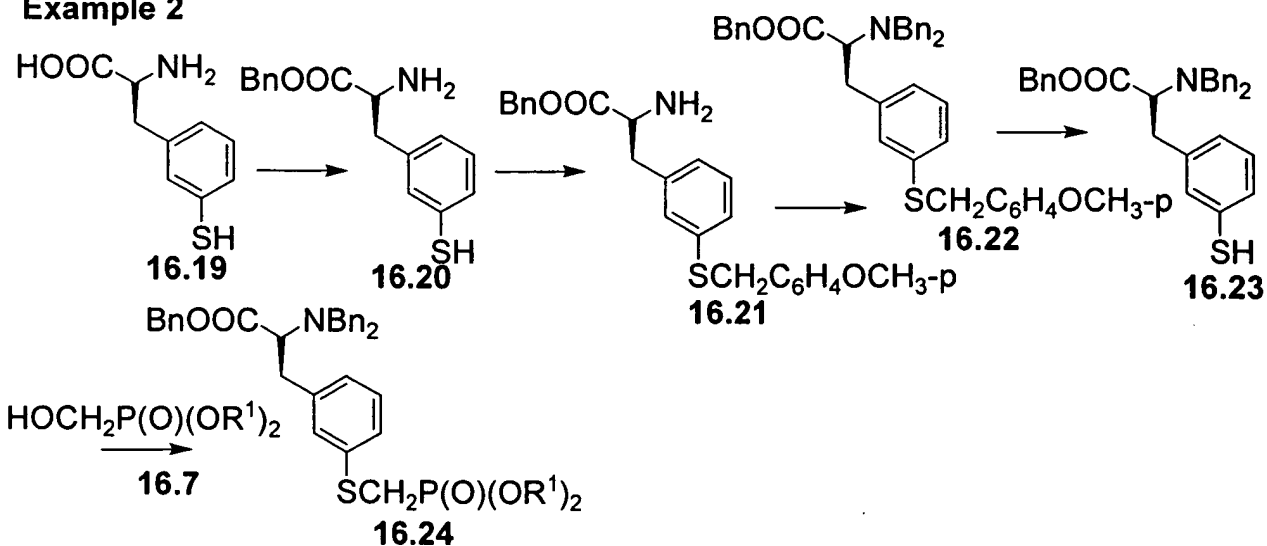
## Method



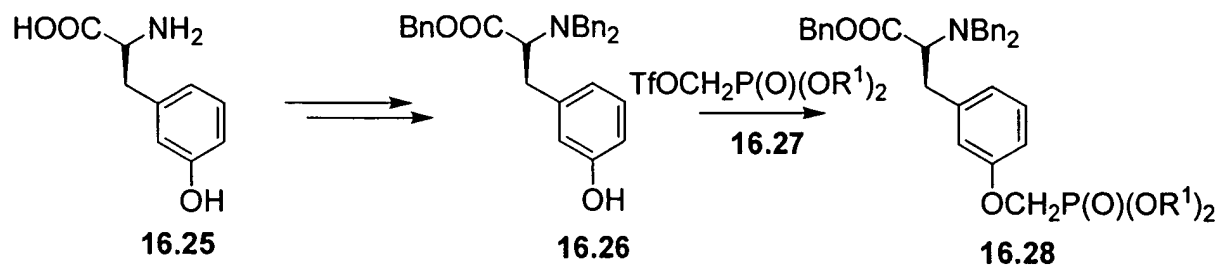
## Example 1



## Example 2

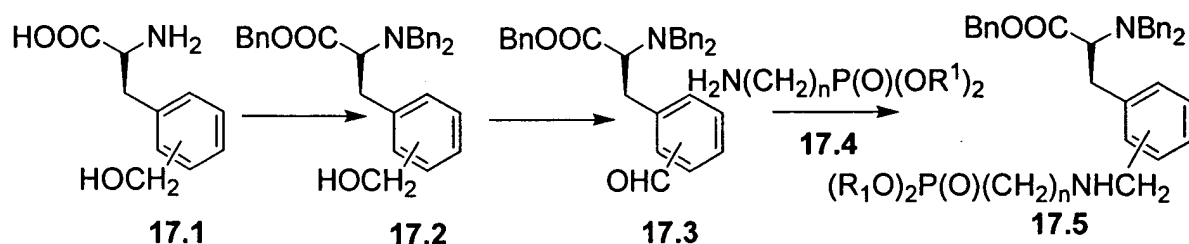


### Example 3

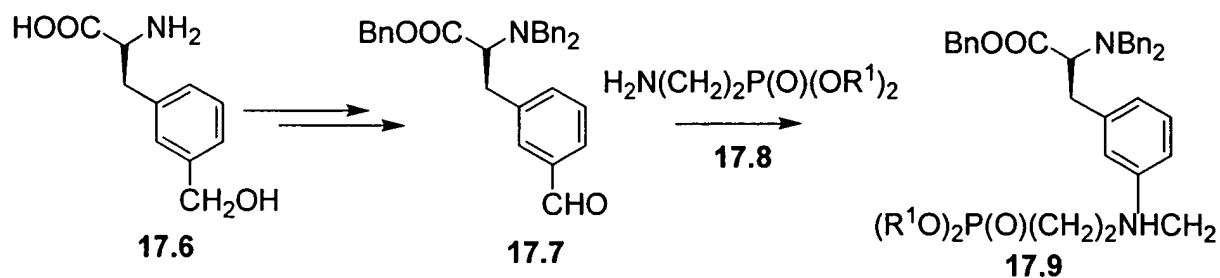


### Scheme 17

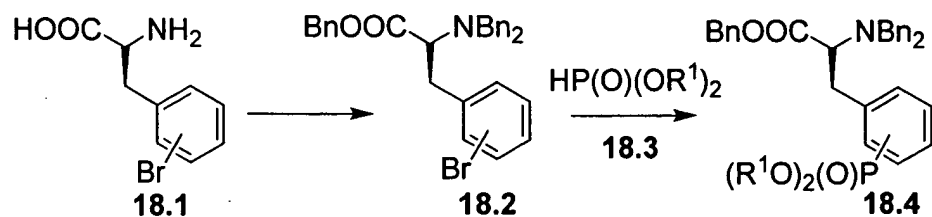
#### Method



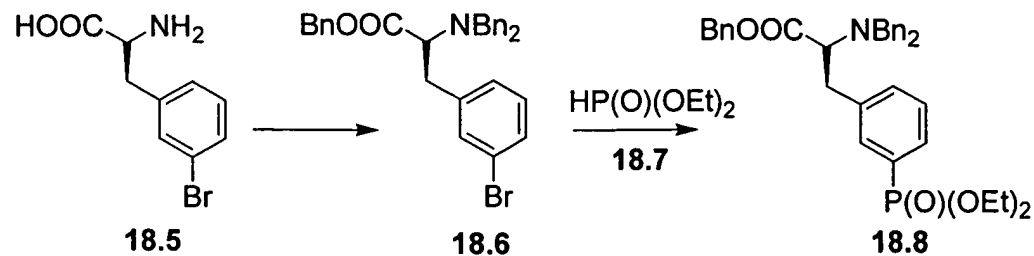
#### Example



### Scheme 18



#### Example



### Preparation of phosphonate esters with structure 3

Scheme 19 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, the ketonitrile 7.1, prepared as described in *J. Org. Chem.*, 1994, 59, 4080, is reacted with a bromobenzylmagnesium halide reagent 19.1. The resultant ketoenamine 19.2 is then converted into the diacylated bromophenyl carbinol 19.3. The conditions required for the conversion of the ketoenamine 19.2 into the carbinol 19.3 are similar to those described above (Scheme 4) for the conversion of the ketoenamine 4.5 into the carbinol 4.12. The product 19.3 is then reacted with a dialkyl phosphite 18.3, in the presence of a palladium (0) catalyst, to yield the phosphonate ester 19.4. The conditions for the coupling reaction are the same as those described above (Scheme 18) for the preparation of the phosphonate ester 18.4.

For example, the ketonitrile 7.1 is reacted, in tetrahydrofuran solution at -40°C, with three molar equivalents of 4-bromobenzylmagnesium bromide 19.5, the preparation of which is described in *Tetrahedron*, 2000, 56, 10067, to afford the ketoenamine 19.6. The latter compound is then converted into the bromophenyl carbinol 19.7, using the sequence of reactions described above (Scheme 4) for the conversion of the ketoenamine 4.5 into the carbinol 4.12. The resultant bromo compound 19.7 is then reacted with diethyl phosphite 18.3 and triethylamine, in toluene solution at reflux, in the presence of tetrakis(triphenylphosphine)palladium(0), as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the phosphonate product 19.8.

Using the above procedures, but employing, in place of 4-bromobenzylmagnesium bromide 19.5, different bromobenzylmagnesium halides 19.1 and/or different dialkyl phosphites 18.3, there are obtained the corresponding phosphonate esters 19.4.

Scheme 20 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached to the nucleus by means of a phenyl ring. In this procedure, a bromophenyl-substituted benzylmagnesium bromide 20.1, prepared from the corresponding bromomethyl compound by reaction with magnesium, is reacted with the ketonitrile 7.1. The conditions for this transformation are the same as those described above (Scheme 4). The product of the Grignard addition reaction is then transformed, using the sequence of reactions described above, (Scheme 4) into the diacylated carbinol 20.2. The latter compound is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 18.3, to afford the

phenylphosphonate **20.3**. The procedure for the coupling reaction is the same as those described above for the preparation of the phosphonate **19.8**.

For example, 4-(4-bromophenyl)benzyl bromide, prepared as described in DE 2262340, is reacted with magnesium to afford 4-(4-bromophenyl)benzylmagnesium bromide **20.4**. This product is then reacted with the ketonitrile **7.1**, as described above, to yield, after the sequence of reactions shown in Scheme 4, the diacylated carbinol **20.5**. The latter compounds then reacted, as described above, (Scheme 18) with a dialkyl phosphite **18.3**, to afford the phenylphosphonate **20.6**.

Using the above procedures, but employing, in place of 4-(4-bromophenyl)benzyl bromide **20.4**, different bromophenylbenzyl bromides **20.1**, and/or different dialkyl phosphites **18.3**, the corresponding products **20.3** are obtained.

Scheme 21 depicts the preparation of phosphonate esters **3** in which the phosphonate group is attached by means of a heteroatom and a methylene group. In this procedure, a hetero-substituted benzyl alcohol **21.1** is protected, affording the derivative **21.2**. The protection of phenyl hydroxyl, thiol and amino groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277, 309. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. Amino groups can be protected, for example by dibenzylation. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Wiley, Second Edition 1990, p. 364. The resultant protected benzyl alcohol **21.1** is converted into a halo derivative **21.2**, in which Ha is chloro or bromo. The conversion of alcohols into chlorides and bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols **21.2** can be transformed into the chloro compounds **21.3**, in which

Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in *J. Am. Chem. Soc.*, 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in *J. Am. Chem. Soc.*, 92, 2139, 1970. The resultant protected benzyl halide **21.3** is then converted into the corresponding benzylmagnesium halide **21.4** by reaction with magnesium metal in an ethereal solvent, or by a Grignard exchange reaction treatment with an alkyl magnesium halide. The resultant substituted benzylmagnesium halide **21.4** is then converted, using the sequence of reactions described above (Scheme 4) for the preparation of the diacylated carbinol **4.11**, into the carbinol **21.5** in which the substituent XH is suitably protected.

The protecting group is then removed to afford the phenol, thiophenol or amine **21.6**. Deprotection of phenols, thiophenols and amines is described respectively in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in *Chem. Pharm. Bull.*, 26, 1576, 1978. N,N-dibenzyl amines can be converted into the unprotected amines by catalytic reduction in the presence of a palladium catalyst, as described above (Scheme 1). The resultant phenol, thiophenol or amine **21.6** is then converted into the phosphonate ester **21.7** by reaction with an activated derivative of a dialkyl hydroxymethyl phosphonate **16.27**, in which Lv is a leaving group. The reaction is conducted under the same conditions as described above for the conversion of **16.5** to **16.11** (Scheme 16).

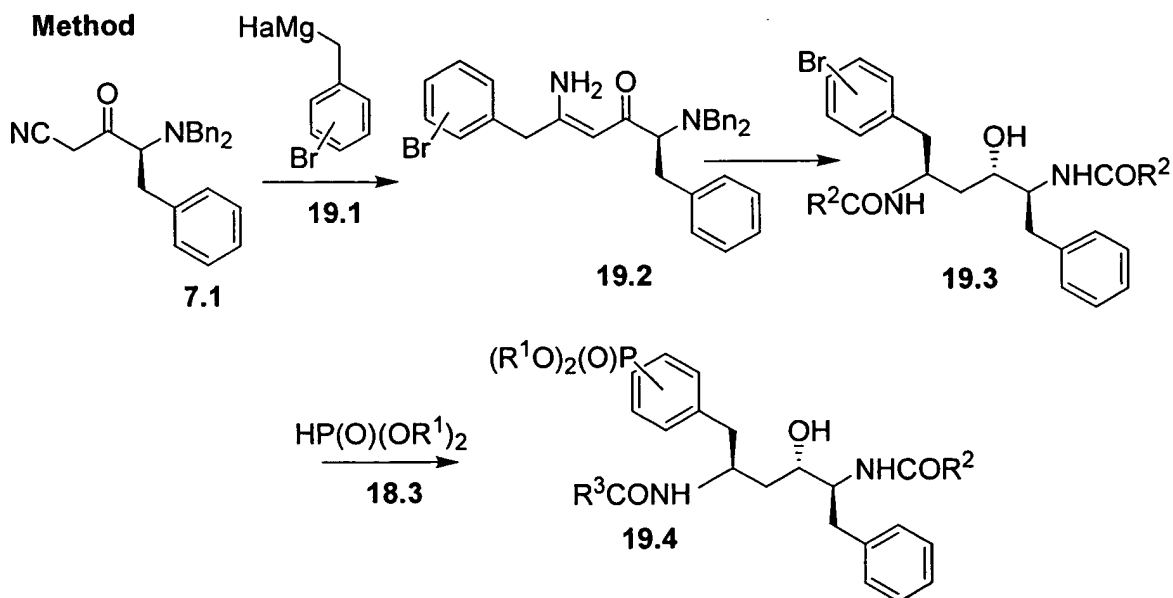
For example, 3-hydroxybenzyl alcohol **21.8** (Aldrich) is reacted with chlorotriisopropylsilane and imidazole in dimethylformamide, as described in *Tetrahedron Lett.*, 2865, 1964, to afford the silyl ether **21.9**. This compound is reacted with carbon tetrabromide and triphenylphosphine in dichloromethane, as described in *J. Am. Chem. Soc.*, 109, 2738, 1987, to afford the brominated product **21.10**. This material is reacted with magnesium in ether to afford the Grignard reagent **21.11**, which is then subjected to the series of reaction shown in Scheme 4 to afford the carbinol **21.12**. The triisopropylsilyl protecting group is then removed by treatment of the ether **21.12** with tetrabutylammonium fluoride in tetrahydrofuran, as described

in *J. Org. Chem.*, 51, 4941, 1986. The resultant phenol **21.13** is then reacted with a dialkyl trifluoromethanesulfonyloxymethylphosphonate **16.27**, prepared as described in *Tetrahedron Lett.*, 1986, 27, 1477, in dimethylformamide solution at 60°C in the presence of cesium carbonate, to afford the phosphonate product **21.14**.

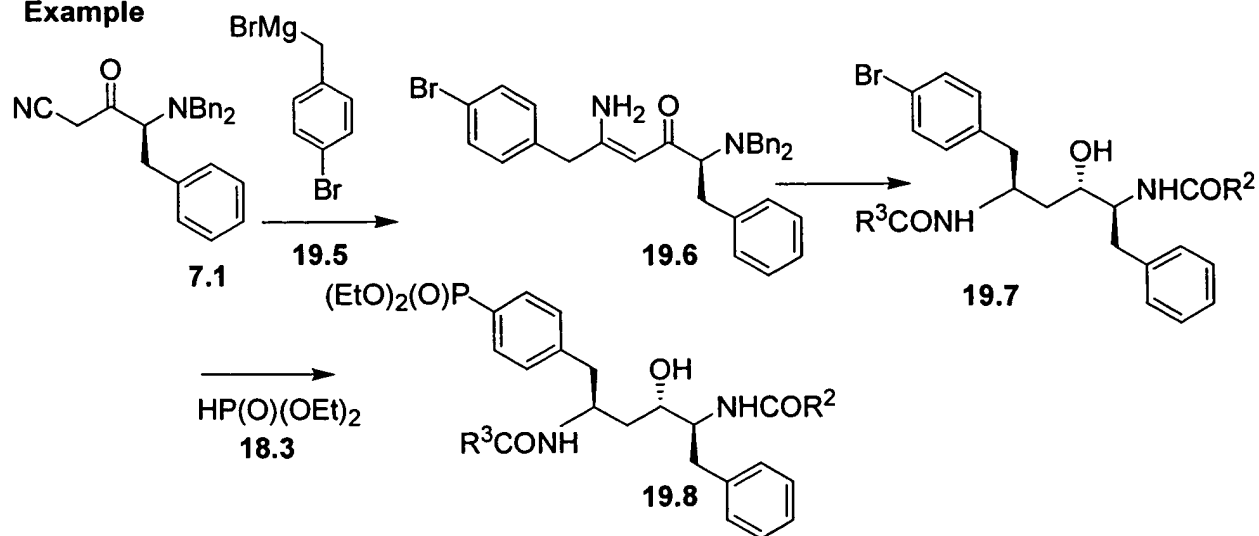
Using the above procedures, but employing, in place of 3-hydroxybenzyl alcohol **21.8**, different hydroxy, mercapto or amino-substituted benzyl alcohols **21.1**, and/or different dialkyl trifluoromethanesulfonyloxymethyl phosphonates **16.27**, the corresponding products **21.7** are obtained.

### Scheme 19

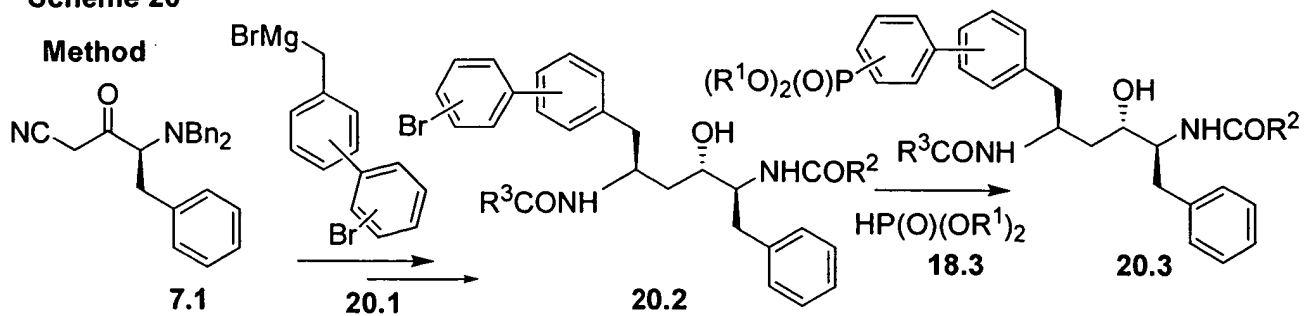
#### Method



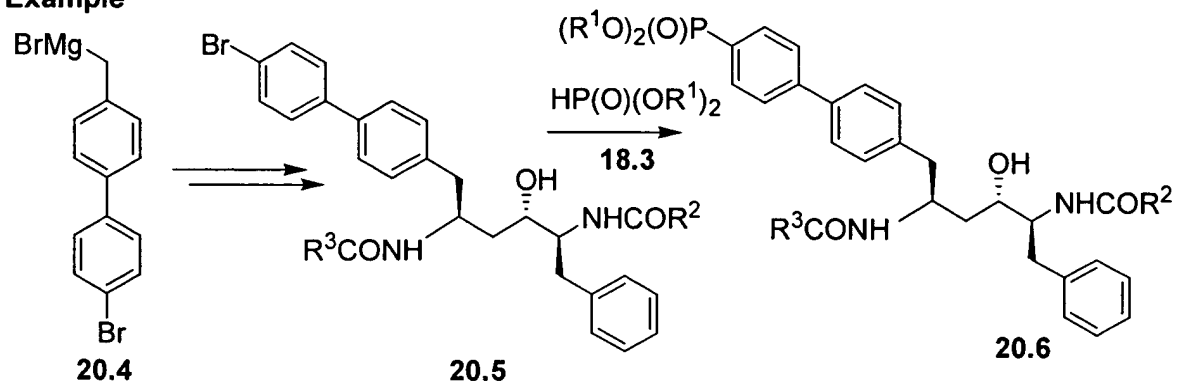
#### Example



# Scheme 20

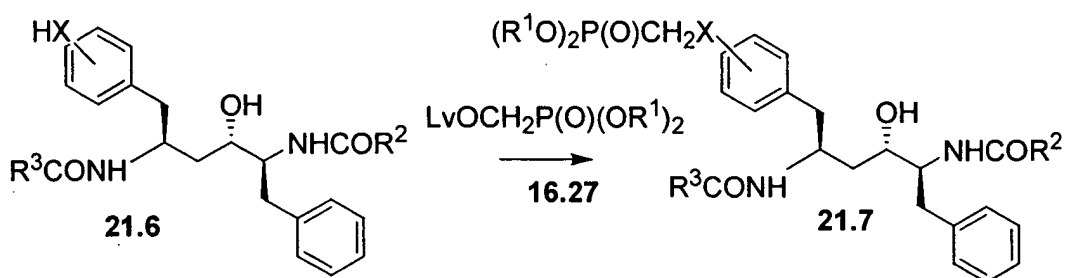
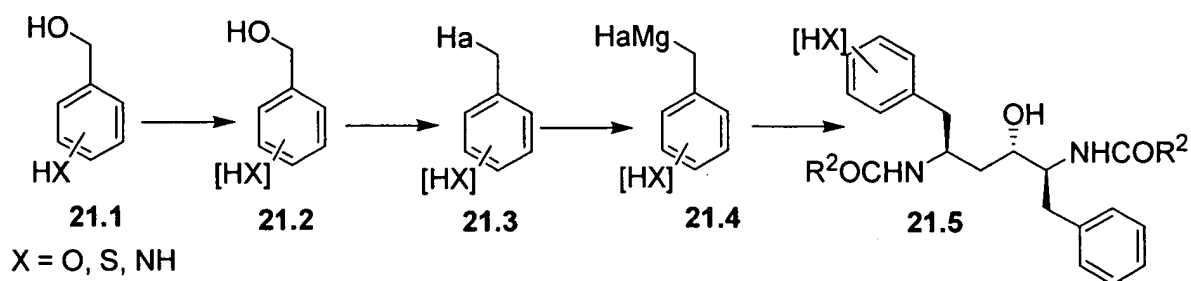


## Example

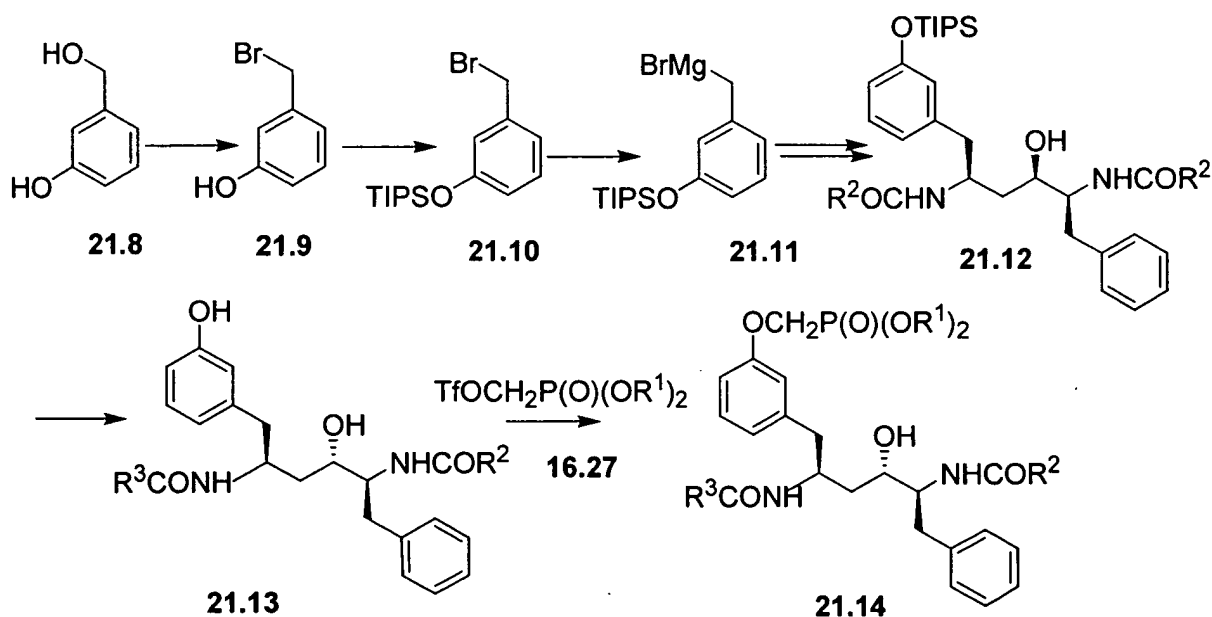


## Scheme 21

### Method



### Example



## Preparation of phosphonate-containing carboxylic acids 1.5

Scheme 22 illustrates methods for the preparation of carboxylic acids 1.5, in which A is Br, and methods for the conversion of the bromo substituent into various phosphonate-containing substituents.

In this procedure, 3-bromo-2-methylpropanamide **22.1** is substituted for the isobutyramide derivative **13.1** in the reaction sequence illustrated in Scheme 13, so as to afford 2-{3-[2-(2-bromo-1-methyl-ethyl)-thiazol-4-ylmethyl]-3-methyl-ureido}-3-methyl-butyric acid methyl ester, **22.2**. The conditions required for the various reactions are the same as those described above (Scheme 13). The bromo-substituted ester **22.2** is then subjected to various transformations so as to introduce phosphonate-containing substituents. For example, the ester **22.2** is reacted with a trialkyl phosphate **22.3** in an Arbuzov reaction, to afford the phosphonate ester **22.4**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in *Handb. Organophosphorus Chem.*, 1992, 115. The reaction is performed by heating the substrate at 100°C to 150°C with an excess of the trialkyl phosphite. The methyl ester group in the phosphonate product **22.4** is then hydrolyzed, using the procedures described above, (Scheme 13) to prepare the carboxylic acid **22.5**.

For example, as shown in Scheme 22, Example 1, the bromo compound **22.2** is heated at 120°C with a ten molar excess of tribenzyl phosphite **22.6** to afford the benzylphosphonate **22.7**. Hydrolysis of the methyl ester, as described above, then yields 2-(3-{2-[2-(bis-benzyloxy-phosphoryl)-1-methyl-ethyl]-thiazol-4-ylmethyl}-3-methyl-ureido)-3-methyl-butyric acid **22.8**.

Alternatively, the bromoester **22.2** is oxidized to the corresponding aldehyde **22.9**. Methods for the oxidation of bromo compounds to the corresponding aldehyde are described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989 p. 599. The transformation can be effected by reaction of the aldehyde with dimethyl sulfoxide, optionally in the presence of a silver salt, as described in *Chem. Rev.*, 67, 247, 1967. Alternatively, the bromo compound is reacted with trimethylamine oxide, as described in *Ber.*, 94, 1360, 1961, to prepare 3-methyl-2-{3-methyl-3-[2-(1-methyl-2-oxo-ethyl)-thiazol-4-ylmethyl]-ureido}-butyric acid methyl ester **22.9**. The aldehyde is then reacted with a dialkyl aminoalkyl phosphonate **22.10** in a reductive amination reaction to afford the aminophosphonate **22.11**. The conditions for the reductive amination reaction are the same as those described above for the preparation of the aminophosphonate **17.5**, (Scheme 17). The methyl ester group present in the product **22.11** is then hydrolyzed, as described above, to yield the carboxylic acid **22.12**.

For example, as shown in Scheme 22, Example 2, the bromo compound **22.2** is heated at 80°C in dimethylsulfoxide solution, in the presence of one molar equivalent of silver tetrafluoroborate and triethylamine, as described in *J. Chem. Soc., Chem. Comm.*, 1338, 1970, to

afford the aldehyde **22.9**. Reductive amination of the product, in the presence of a dialkyl aminoethyl phosphonate **22.13**, the preparation of which is described in *J. Org. Chem.*, 2000, 65, 676 and sodium triacetoxy borohydride, then affords the amino phosphonate **22.14**. Hydrolysis of the methyl ester, as described above, then afford the carboxylic acid **22.15**.

Alternatively, the bromo compound **22.2** is reacted with a dialkyl thioalkyl phosphonate **22.16** to effect displacement of the bromo substituent to afford the thioether **22.17**. The preparation of thioethers by the reaction of bromo compounds with thiols is described, for example, in *Synthetic Organic Chemistry*, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reactants are combined in the presence of a suitable base, such as sodium hydroxide, dimethylaminopyridine, potassium carbonate and the like, in a polar organic solvent such as dimethylformamide or ethanol, to afford the thioether **22.17**. The product is then subjected to hydrolysis, as described above, to afford the carboxylic acid **22.18**.

For example, as shown in Scheme 22, Example 3, the bromo compound **22.2** is reacted with a dialkyl thioethylphosphonate **22.19**, the preparation of which is described in *Aust. J. Chem.*, 43, 1123, 1990, and dimethylaminopyridine, in dimethylformamide solution at ambient temperature, to yield the thioether **22.20**. Hydrolysis of the methyl ester group, as described above, then afford the carboxylic acid **22.21**.

Scheme 23 illustrates the preparation of carboxylic acids **23.7** in which the phosphonate moiety is attached to the isopropyl group by means of a phenyl ring and a heteroatom. In this procedure, the hydroxy or mercapto substituent on a phenylbutanamide **23.1** is protected. Methods for the protection of hydroxyl and thiol groups are described above (Scheme 21). The protected amide **23.2** is then subjected to the series of reactions illustrated in Scheme 13, so as to afford the O- or S-protected ester **23.3**. The protecting group is then removed. Methods for the deprotection of phenols and thiophenols are described above (Scheme 16). The resultant phenol or thiophenol **23.4** is then reacted with a dialkyl bromoalkyl phosphonate **23.5**, to afford the ether or thioether compounds **23.6**. Conditions for the alkylation of phenols and thiophenols are described above (Scheme 16). The ester groups present in the product **23.6** is then hydrolyzed, as described above, to afford the corresponding carboxylic acid **23.7**.

For example, 3-(4-hydroxyphenyl)butyric acid **23.8**, prepared as described in *J. Med. Chem.*, 1992, 35, 548, is converted into the acid chloride by reaction with thionyl chloride. The acid chloride is then reacted with excess aqueous ethanolic ammonia to afford the amide **23.9**.

This compound is converted into the tert. butyldimethylsilyl derivative **23.10** by treatment with tert-butylchlorodimethylsilane and imidazole in dichloromethane. The resultant amide **23.10** is then subjected to the series of reactions shown in Scheme 13, so as to yield the ester **23.11**.

Desilylation, by treatment with tetrabutylammonium fluoride in tetrahydrofuran, then affords the phenol **23.12**. This compound is reacted with a dialkyl bromoethyl phosphonate **23.13** (Aldrich) and potassium carbonate, in dimethylformamide at 80°C, to produce the ether **23.14**. Hydrolysis of the ester group, by treatment with aqueous methanolic lithium hydroxide, then affords the carboxylic acid **23.15**.

Using the above procedures, but employing, in place of the amide **23.9**, different hydroxy- or thio-substituted amides **23.23.1**, and/or different bromoalkylphosphonates **23.5**, the corresponding products **23.7** are obtained.

Scheme 24 and 25 describes the preparation of carboxylic acids **9.1** in which the phosphonate moiety is attached to the amine component. In this procedure, the chloromethylthiazole **14.1**, is reacted with a dialkyl aminoalkyl phosphonate **24.1** to produce the substituted amine **24.2**. The preparation of amines by reacting amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Typically, the components are reacted together in a polar solvent such as an alkanol or dimethylformamide and the like, to yield the substituted amine **24.2**. The latter compound is then converted into the carboxylic acid **24.3**, by means of the series of reactions shown in Scheme 14.

For example, the chloromethyl thiazole **14.1** is reacted at 50°C in acetonitrile solution containing potassium carbonate, with one molar equivalent of a dialkyl aminomethyl phosphonate **24.4**, prepared as described in *Bioorg. Chem.*, 2001, 29, 77, to afford the substituted amine **24.5**. The product is then converted, using the reactions shown in Scheme 14, into the carboxylic acid **24.6**.

Using the above procedures, but employing, in place of the dialkyl aminoethyl phosphonate **24.4**, different dialkyl aminoalkyl phosphonates **24.1**, the corresponding products **24.3** are obtained.

Scheme 25 illustrates the preparation of carboxylic acids **9.1** in which the phosphonate moiety is attached to the amine component by means of a saturated or unsaturated alkyl chain and a phenyl ring. In this procedure, the chloromethylthiazole **14.1** is reacted with allylamine

**25.1**, using the procedures described above (Scheme **24**) to afford allyl-(2-isopropyl-thiazol-4-ylmethyl)-amine **25.2**. The ester amine is then converted, by means of the series of reactions shown in Scheme **14**, into 2-[3-allyl-3-(2-isopropyl-thiazol-4-ylmethyl)-ureido]-3-methyl-butyric acid methyl ester **25.3**. This material is coupled with a dialkyl bromo-substituted phenylphosphonate **25.4**, under the conditions of the palladium-catalyzed Heck reaction, to afford the coupled product **25.5**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Hydrolysis of the methyl ester, as described above, then yields the carboxylic acid **25.6**. Optionally, the double bond present in the product **25.6** is reduced to afford the dihydro analog **25.7**. The double bond is reduced in the presence of a palladium catalyst, such as, for example, 5% palladium on carbon, in a solvent such as methanol or ethanol, to afford the product **25.7**.

For example, the allyl-substituted urea **25.3** is reacted with a dialkyl 4-bromophenyl phosphonate **25.8**, prepared as described in *J. Chem. Soc., Perkin Trans.*, 1977, 2, 789 in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to afford the phosphonate ester **25.9**. Ester hydrolysis, as described above, then affords the carboxylic acid **25.10**. Hydrogenation, as described above, then affords the saturated analog **25.11**.

Using the above procedures, but employing, in place of the 4-bromophenyl phosphonate **25.8**, different bromophenyl phosphonates **25.4**, the corresponding products **25.6** and **25.7** are obtained.

Scheme **26** illustrates the preparation of carboxylic acids **11.1** in which the phosphonate moiety is attached to the valine substructure. In this procedure, 2-amino-4-bromo-3-methyl-butyric acid methyl ester **26.1**, prepared as described in U.S. Patent 5,346,898, is reacted with a chloroformate, for example 4-nitrophenyl chloroformate, to prepare the activated derivative **26.2** in which X is a leaving group. For example, the aminoester **26.1** is reacted with 4-nitrophenylchloroformate in dichloromethane at 0°C, as described in U.S. 5,484,801, to afford the product **26.2** in which X is 4-nitrophenoxy. The latter compound is reacted with (2-isopropyl-thiazol-4-ylmethyl)-methyl-amine **26.3**, prepared as described in U.S. 5,484,801, in the

presence of a base such as triethylamine or dimethylaminopyridine, in an inert solvent such as dichloromethane or tetrahydrofuran, to afford 4-bromo-2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-butyric acid methyl ester **26.4**. The bromo compound **26.4** is then oxidized to afford the aldehyde **26.5**. The oxidation of bromo compounds to afford the corresponding aldehydes is described above (Scheme 22). In a typical procedure, the bromo compound is heated at 80°C in dimethylsulfoxide solution, optionally in the presence of silver salt such as silver perchlorate or silver tetrafluoroborate, as described in *J. Am. Chem. Soc.*, 81, 4113, 1959, to afford 2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-4-oxo-butyric acid methyl ester **26.5**. The aldehyde is then subjected to a reductive amination procedure, in the presence of a dialkyl aminoalkyl phosphonate **26.6**, to afford the amine product **26.7**. The preparation of amines by means of reductive alkylation reactions is described above (Scheme 22). Equimolar amounts of the aldehyde **26.5** and the amine **26.6** are reacted in the presence of a boron-containing reducing agent such as, for example, sodium triacetoxyborohydride, to yield the amine **26.7**. The methyl ester is then hydrolyzed, as described above, to yield the carboxylic acid **26.8**.

For example, 2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-4-oxo-butyric acid methyl ester **26.5** is reacted with a dialkyl aminoethylphosphonate **26.9** and sodium cyanoborohydride, to afford the amine product **26.10**. The methyl ester is then hydrolyzed, as described above to yield the carboxylic acid **26.11**.

Using the above procedures, but employing, in place of the dialkyl aminoethylphosphonate **26.9**, different aminoalkyl phosphonates **26.6**, the corresponding products **26.8** are obtained.

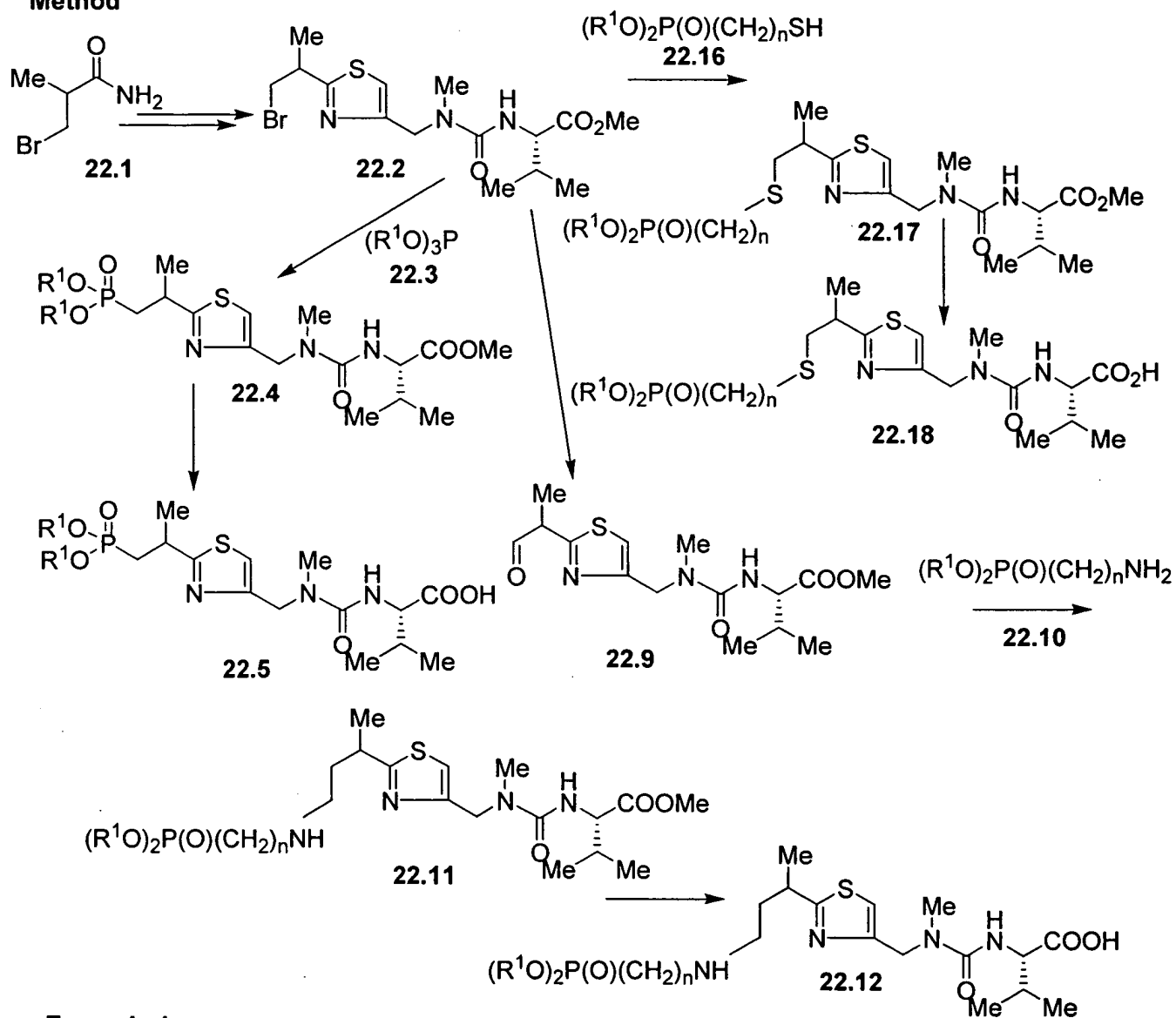
Alternatively, the bromo-substituted methyl ester **26.4** is then reacted with a dialkyl mercaptoalkyl phosphonate **26.12** to afford the thioether **26.13**. The preparation of thioethers by the reaction of bromo compounds with thiols is described, for example, in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reactants are combined in the presence of a suitable base, such as sodium hydroxide, dimethylamino pyridine, potassium or cesium carbonate and the like, in a polar organic solvent such as dimethylformamide or ethanol, to afford the thioether **26.13**. The methyl ester is then hydrolyzed, as described above to yield the carboxylic acid **26.14**.

For example, the bromo compound **26.4** is reacted with a dialkyl mercaptoethyl phosphonate **26.15**, the preparation of which is described in *Aust. J. Chem.*, 43, 1123, 1990, in dimethylformamide solution, in the presence of cesium carbonate, to produce the thio ether product **26.16**. The methyl ester is then hydrolyzed, as described above, to yield the carboxylic acid **26.17**.

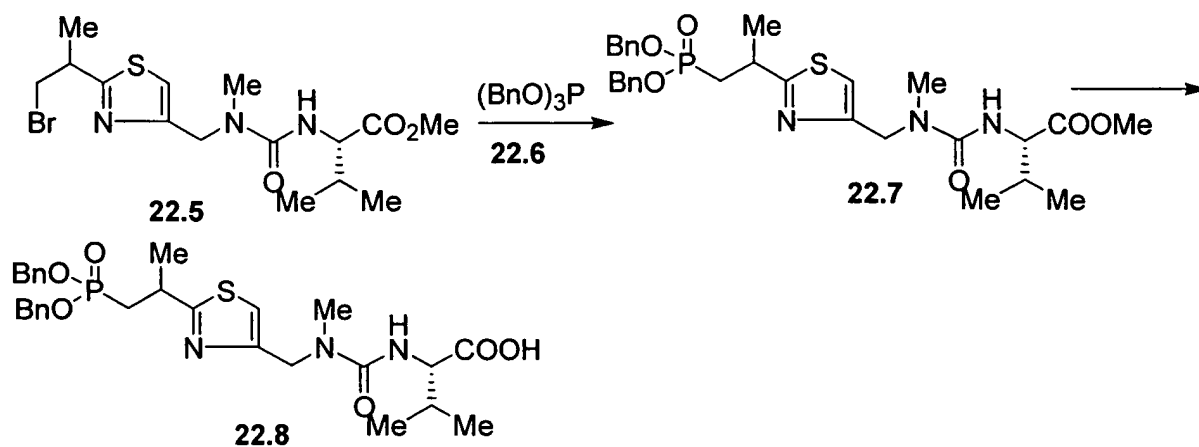
Using the above procedures, but employing, in place of the dialkyl mercaptoethyl phosphonate **26.15**, different mercaptoalkyl phosphonates **26.12**, the corresponding products **26.14** are obtained.

# Scheme 22

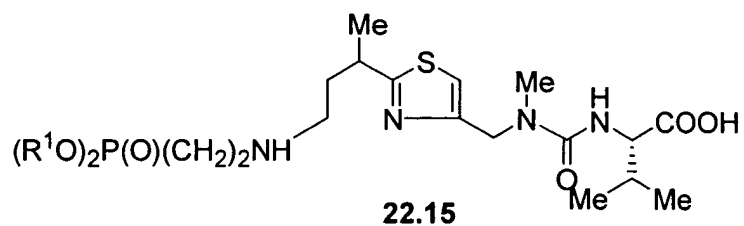
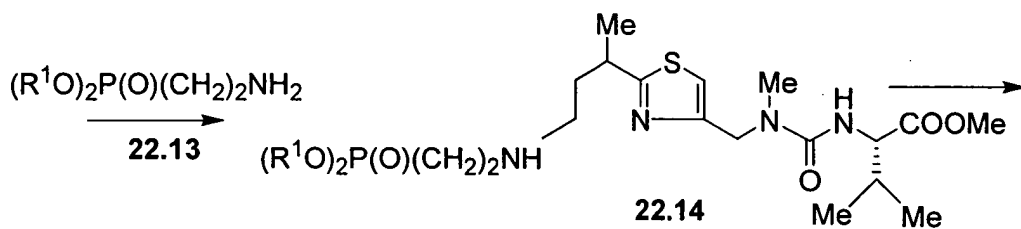
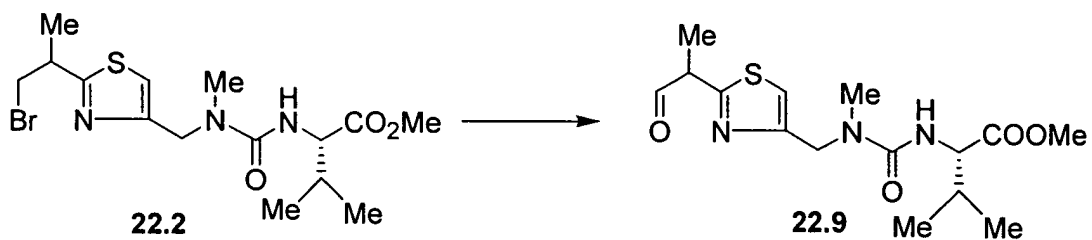
## Method



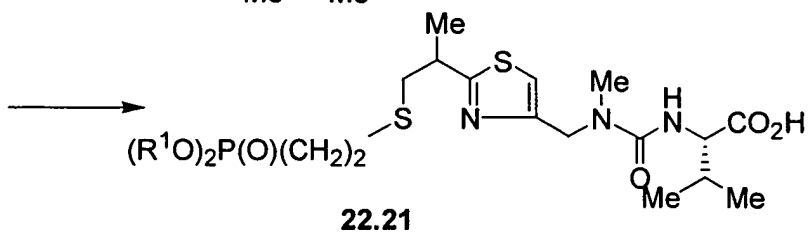
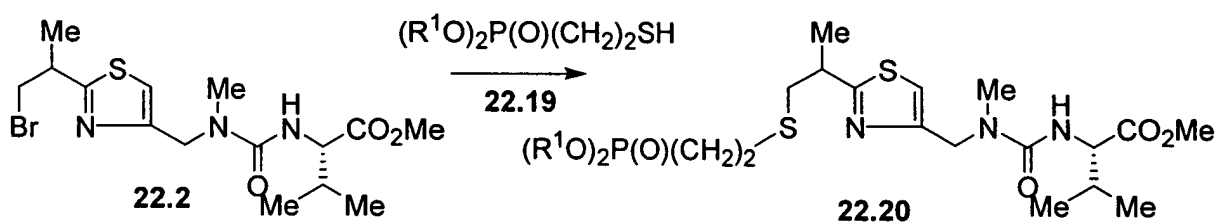
## Example 1



### Example 2

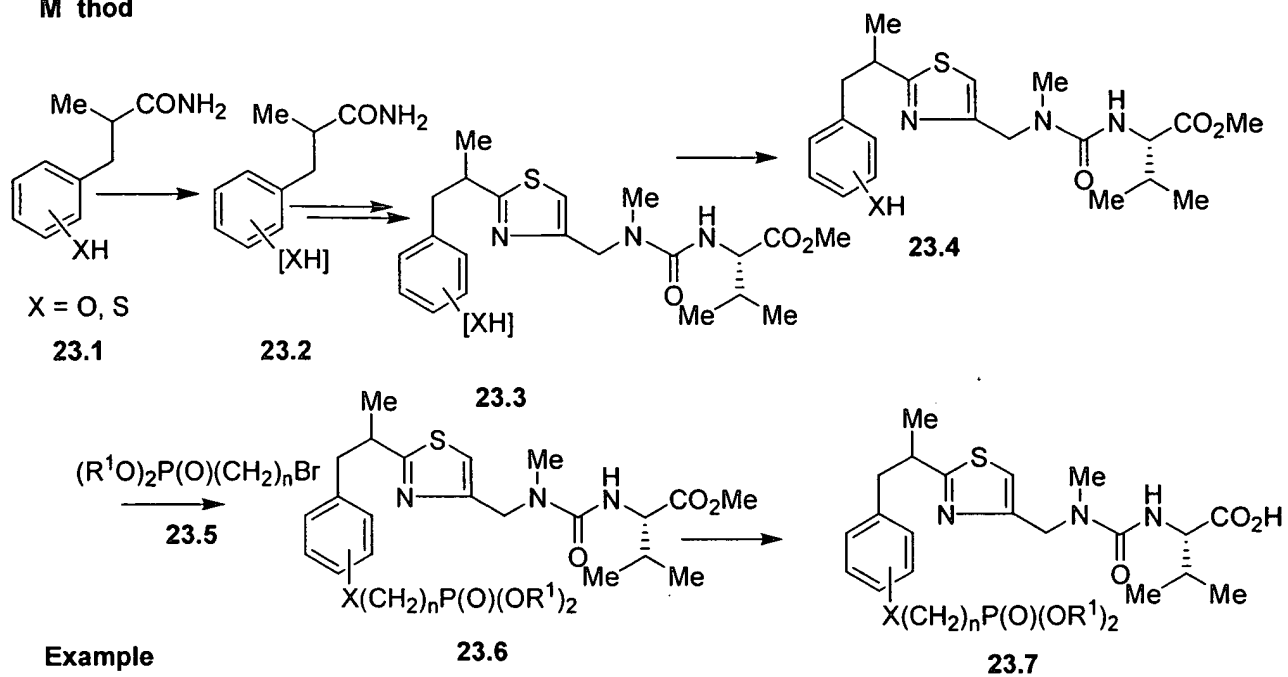


### Example 3

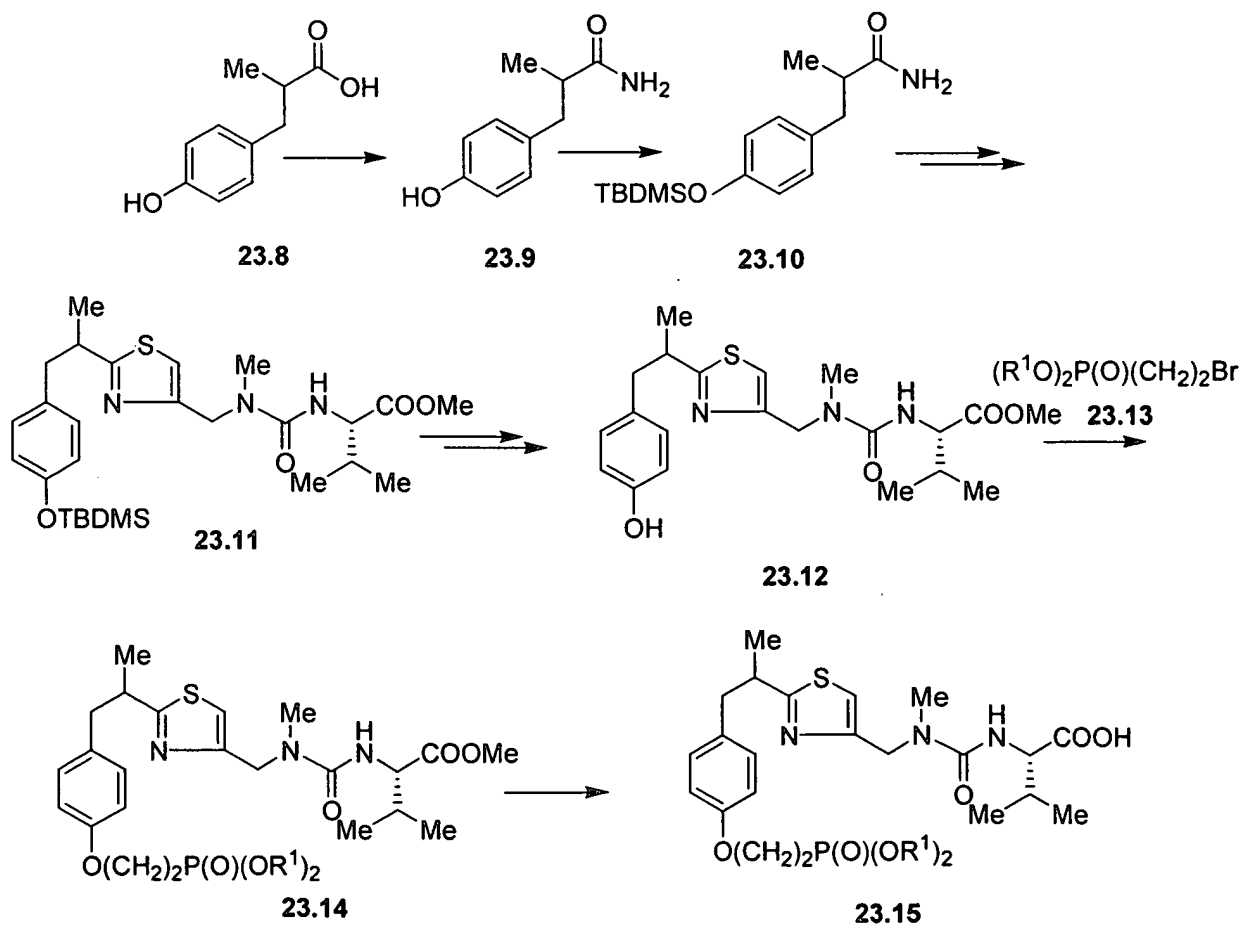


# Scheme 23

## Method

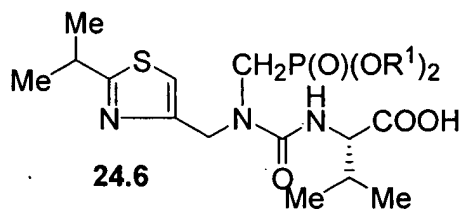
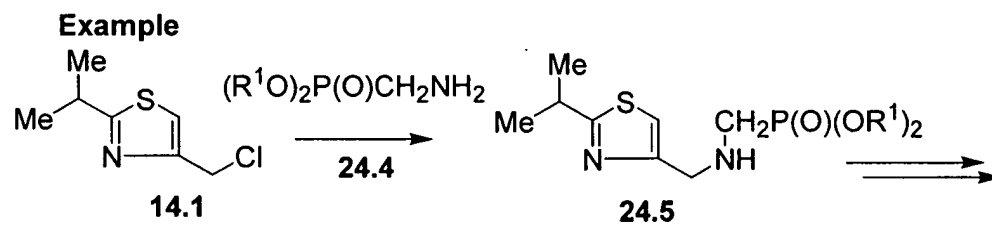
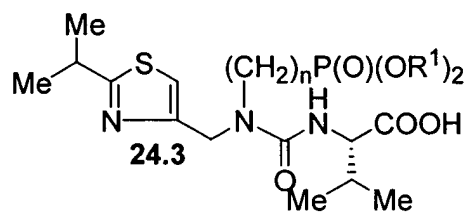
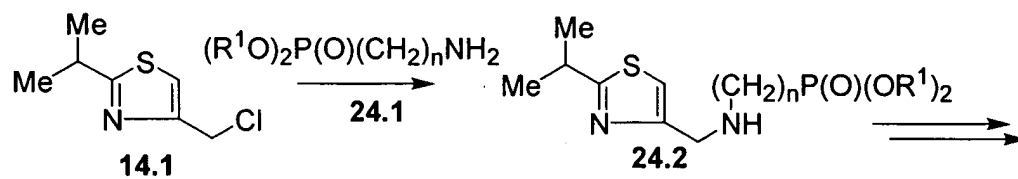


## Example

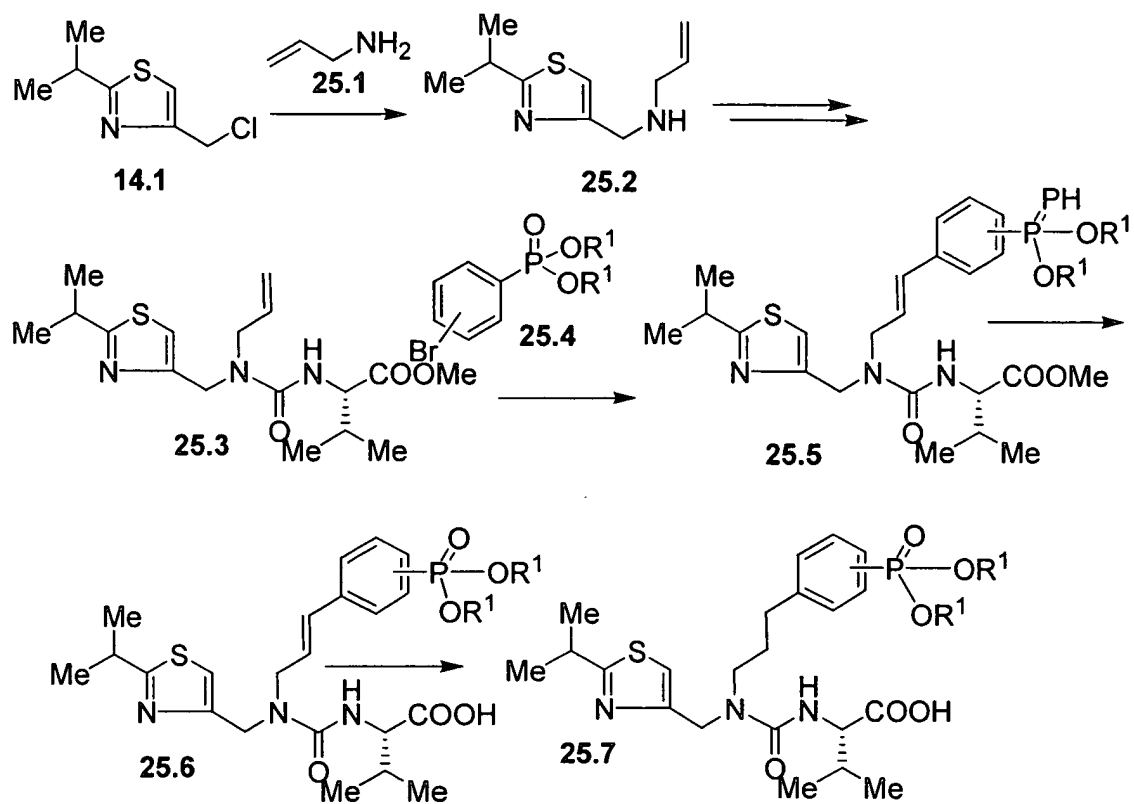


## Scheme 24

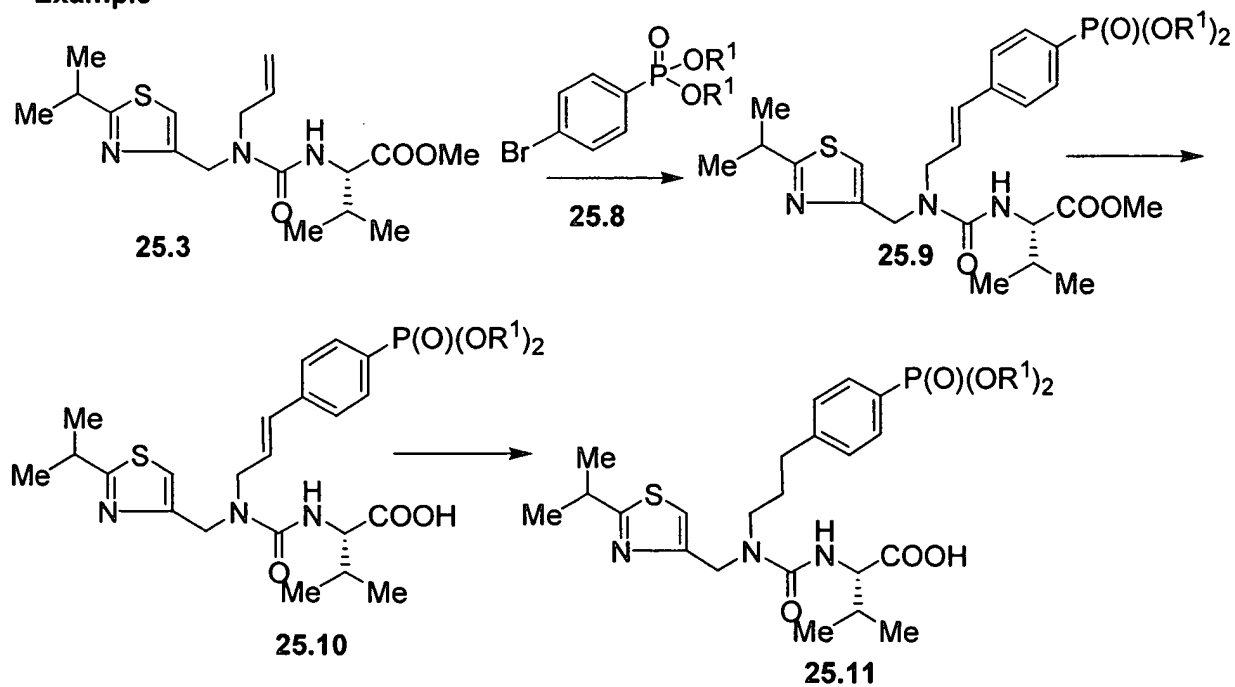
### Method



**Scheme 25**  
**Method**

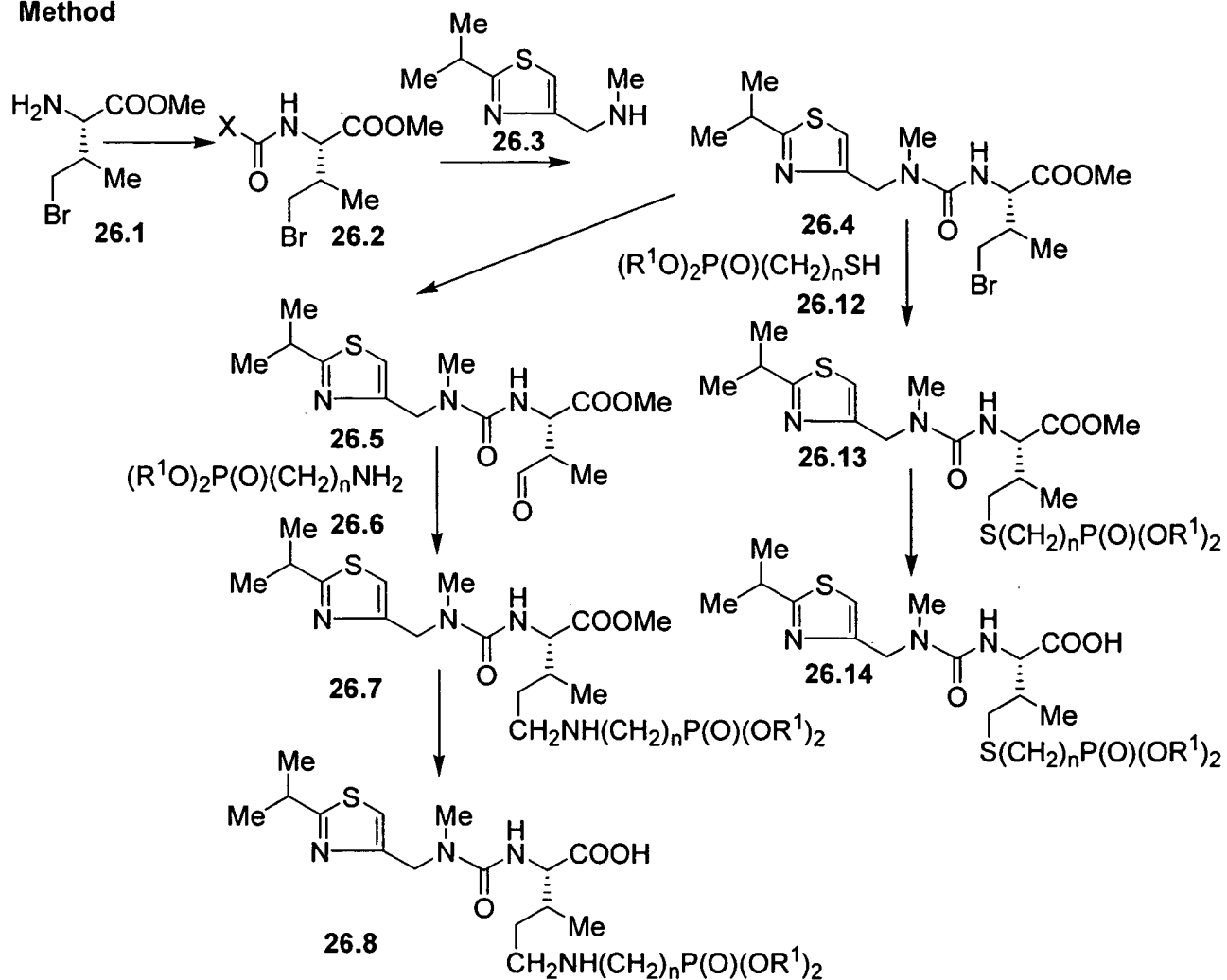


**Example**

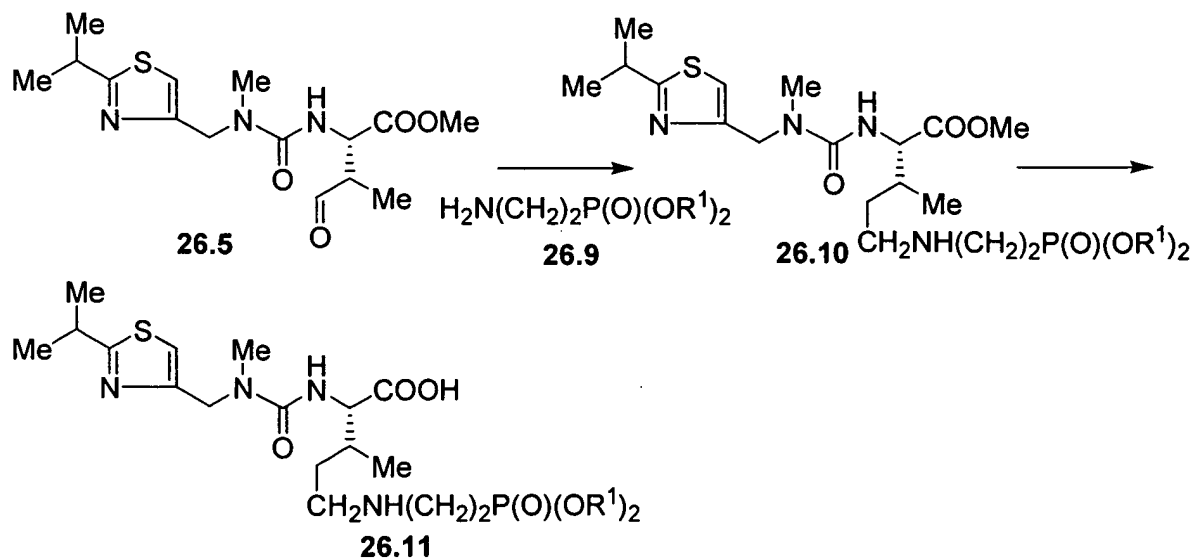


# Scheme 26

## Method



## Example 1



### Interconversions of the phosphonates

#### R-link-P(O)(OR<sup>1</sup>)<sub>2</sub>, R-link-P(O)(OR<sup>1</sup>)(OH) and R-link-P(O)(OH)<sub>2</sub>

Schemes 1-26 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR<sup>1</sup>)<sub>2</sub>, in which the groups R<sup>1</sup>, the structures of which are defined in Chart 1, may be the same or different. The R<sup>1</sup> groups attached to a phosphonate esters 1-7, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 27. The group R in Scheme 27 represents the substructure to which the substituent link-P(O)(OR<sup>1</sup>)<sub>2</sub> is attached, either in the compounds 1-7 or in precursors thereto. The R<sup>1</sup> group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-7. The methods employed for a given phosphonate transformation depend on the nature of the substituent R<sup>1</sup>. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 27.1 into the corresponding phosphonate monoester 27.2 (Scheme 27, Reaction 1) can be accomplished by a number of methods. For example, the ester 27.1 in which R<sup>1</sup> is an aralkyl group such as benzyl, can be converted into the monoester compound 27.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 27.1 in which R<sup>1</sup> is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 27.2 can be effected by treatment of the ester 27.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 27.1 in which one of the groups R<sup>1</sup> is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 27.2 in which R<sup>1</sup> is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R<sup>1</sup> are alkenyl, such as allyl, can be converted into the monoester 27.2 in which R<sup>1</sup> is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.*, 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 27.1 or a phosphonate monoester 27.2 into the corresponding phosphonic acid 27.3 (Scheme 27, Reactions 2 and 3) can be effected by reaction of

the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which R<sup>1</sup> is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **27.2** in which R<sup>1</sup> is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which R<sup>1</sup> is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **27.1** in which R<sup>1</sup> is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme 27, Reaction 4) in which the newly introduced R<sup>1</sup> group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **27.2** is reacted with a hydroxy compound R<sup>1</sup>OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **27.2** to the diester **27.1** can be effected by the use of the Mitsunobu reaction, as described above (Scheme 16). The substrate is reacted with the hydroxy compound R<sup>1</sup>OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **27.2** can be transformed into the phosphonate diester **27.1**, in which the introduced R<sup>1</sup> group is alkenyl or aralkyl, by reaction of the monoester with the halide R<sup>1</sup>Br, in which R<sup>1</sup> is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or

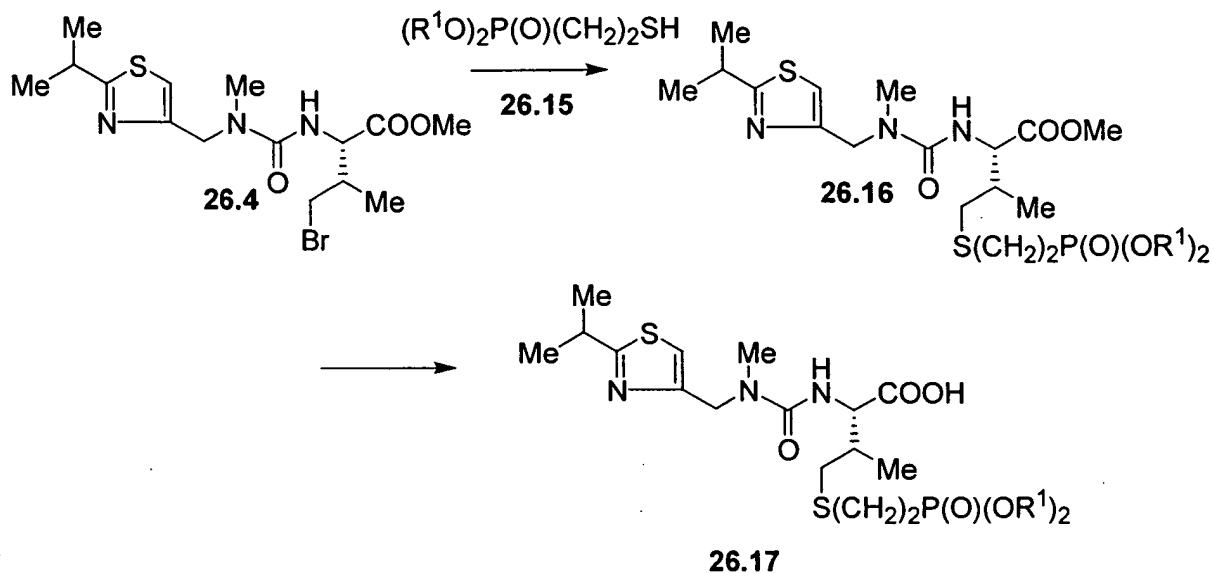
acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **27.2** is transformed into the chloro analog  $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$  by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product  $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$  is then reacted with the hydroxy compound  $\text{R}^1\text{OH}$ , in the presence of a base such as triethylamine, to afford the phosphonate diester **27.1**.

A phosphonic acid  $\text{R-link-P}(\text{O})(\text{OH})_2$  can be transformed into a phosphonate monoester  $\text{RP}(\text{O})(\text{OR}^1)(\text{OH})$  (Scheme 27, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester  $\text{R-link-P}(\text{O})(\text{OR}^1)_2$  **27.1**, except that only one molar proportion of the component  $\text{R}^1\text{OH}$  or  $\text{R}^1\text{Br}$  is employed.

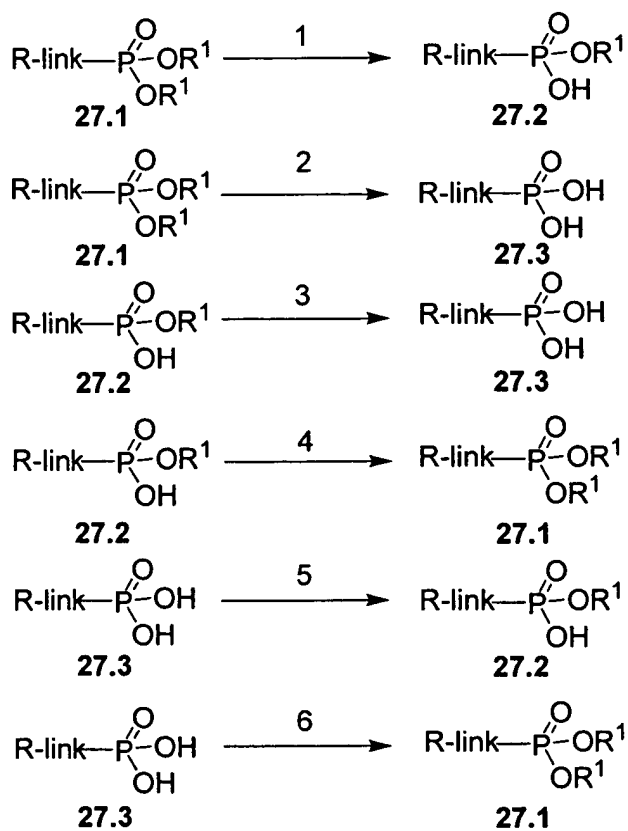
A phosphonic acid  $\text{R-link-P}(\text{O})(\text{OH})_2$  **27.3** can be transformed into a phosphonate diester  $\text{R-link-P}(\text{O})(\text{OR}^1)_2$  **27.1** (Scheme 27, Reaction 6) by a coupling reaction with the hydroxy compound  $\text{R}^1\text{OH}$ , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which  $\text{R}^1$  is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca  $70^\circ\text{C}$ . Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which  $\text{R}^1$  is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide  $\text{R}^1\text{Br}$  in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **27.1**.

# Scheme 26

## Example 2



# Scheme 27



### General applicability of methods for introduction of phosphonate substituents

The procedures described above for the conversion of various functional groups into phosphonate moieties are of general application. For example, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety, can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the thiazole compounds **1.5**, **9.1** and **11.1**, and for the preparation of the phosphonate esters **3**. Similarly, the methods described above for the introduction of phosphonate groups into the thiazole compounds **1.5**, **9.1** and **11.1** can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine intermediates **4.1** and for the preparation of the compounds **3**.

### Phosphonate esters 1-7 incorporating carbamate moieties

The phosphonate esters **1-7** in which the  $R^2CO$  or  $R^3CO$  groups are formally derived from the carboxylic acid synthons **14-16**, **19**, **21**, **22**, **25**, **34**, **51** or **52** as shown in Charts **2a**, **2b**, and **2c**, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **28** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **28**, in the general reaction generating carbamates, a carbinol **28.1** is converted into the activated derivative **28.2** in which  $L_v$  is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **28.2** is then reacted with an amine **28.3**, to afford the carbamate product **28.4**. Examples **1 – 7** in Scheme **28** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **28**, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **28.5**. In this procedure, the carbinol **28.5** is reacted with phosgene, in an inert solvent such as toluene, at about  $0^\circ\text{C}$ , as described in *Org. Syn. Coll.* Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in *Org. Syn. Coll.* Vol. 6, 715, 1988, to afford the chloroformate **28.6**. The latter compound is then reacted with the amine component **28.3**, in the presence of an organic or inorganic base, to afford the carbamate **28.7**. cFor example, the chloroformyl compound **28.6** is reacted with the

amine **28.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in *Org. Syn. Coll.* Vol. 3, 167, 1965, to yield the carbamate **28.7**. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **28**, Example **2** depicts the reaction of the chloroformate compound **28.6** with imidazole, **28.7**, to produce the imidazolide **28.8**. The imidazolide product is then reacted with the amine **28.3** to yield the carbamate **28.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in *J. Med. Chem.*, 1989, 32, 357.

Scheme **28** Example **3**, depicts the reaction of the chloroformate **28.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **28.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **28.19** - **28.24** shown in Scheme **28**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **28.19**, N-hydroxysuccinimide **28.20**, or pentachlorophenol, **28.21**, the mixed carbonate **28.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in *Can. J. Chem.*, 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **28.22** or 2-hydroxypyridine **28.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in *Synthesis*, 1986, 303, and *Chem. Ber.* 118, 468, 1985.

Scheme **28** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **28.8** is employed. In this procedure, a carbinol **28.5** is reacted with an equimolar amount of carbonyl diimidazole **28.11** to prepare the intermediate **28.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **28.8** is then reacted with an equimolar amount of the amine R'NH<sub>2</sub> to afford the carbamate **28.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in *Tetrahedron Lett.*, 42, 2001, 5227, to afford the carbamate **28.7**.

Scheme 28, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **28.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **28.12**, to afford the alkoxycarbonyl product **28.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in *Synthesis*, 1977, 704. This product is then reacted with the amine R'NH<sub>2</sub> to afford the carbamate **28.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in *Synthesis*, 1977, 704.

Scheme 28, Example 6 illustrates the preparation of carbamates in which a carbonate (R''O)<sub>2</sub>CO, **28.14**, is reacted with a carbinol **28.5** to afford the intermediate alkyloxycarbonyl intermediate **28.15**. The latter reagent is then reacted with the amine R'NH<sub>2</sub> to afford the carbamate **28.7**. The procedure in which the reagent **28.15** is derived from hydroxybenztriazole **28.19** is described in *Synthesis*, 1993, 908; the procedure in which the reagent **28.15** is derived from N-hydroxysuccinimide **28.20** is described in *Tetrahedron Lett.*, 1992, 2781; the procedure in which the reagent **28.15** is derived from 2-hydroxypyridine **28.23** is described in *Tetrahedron Lett.*, 1991, 4251; the procedure in which the reagent **28.15** is derived from 4-nitrophenol **28.24** is described in *Synthesis* 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **28.14** is conducted in an inert organic solvent at ambient temperature.

Scheme 28, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides **28.16**. In this procedure, an alkyl chloroformate **28.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **28.16**. The latter compound is then reacted with an equimolar amount of the amine R'NH<sub>2</sub> to afford the carbamate **28.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in *Synthesis*, 1982, 404.

Scheme 28, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in *Synthetic Organic Chemistry*, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **28.7**.

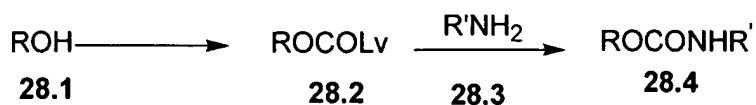
Scheme 28, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **28.18**. In this procedure, which is described in

Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **28.7**.

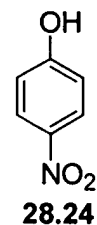
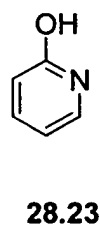
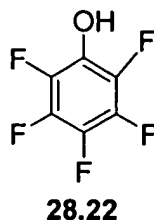
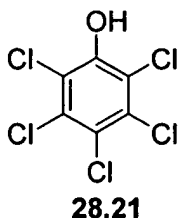
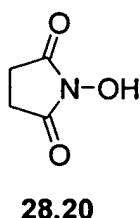
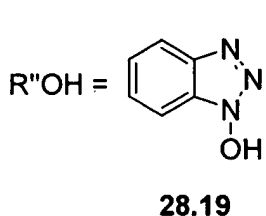
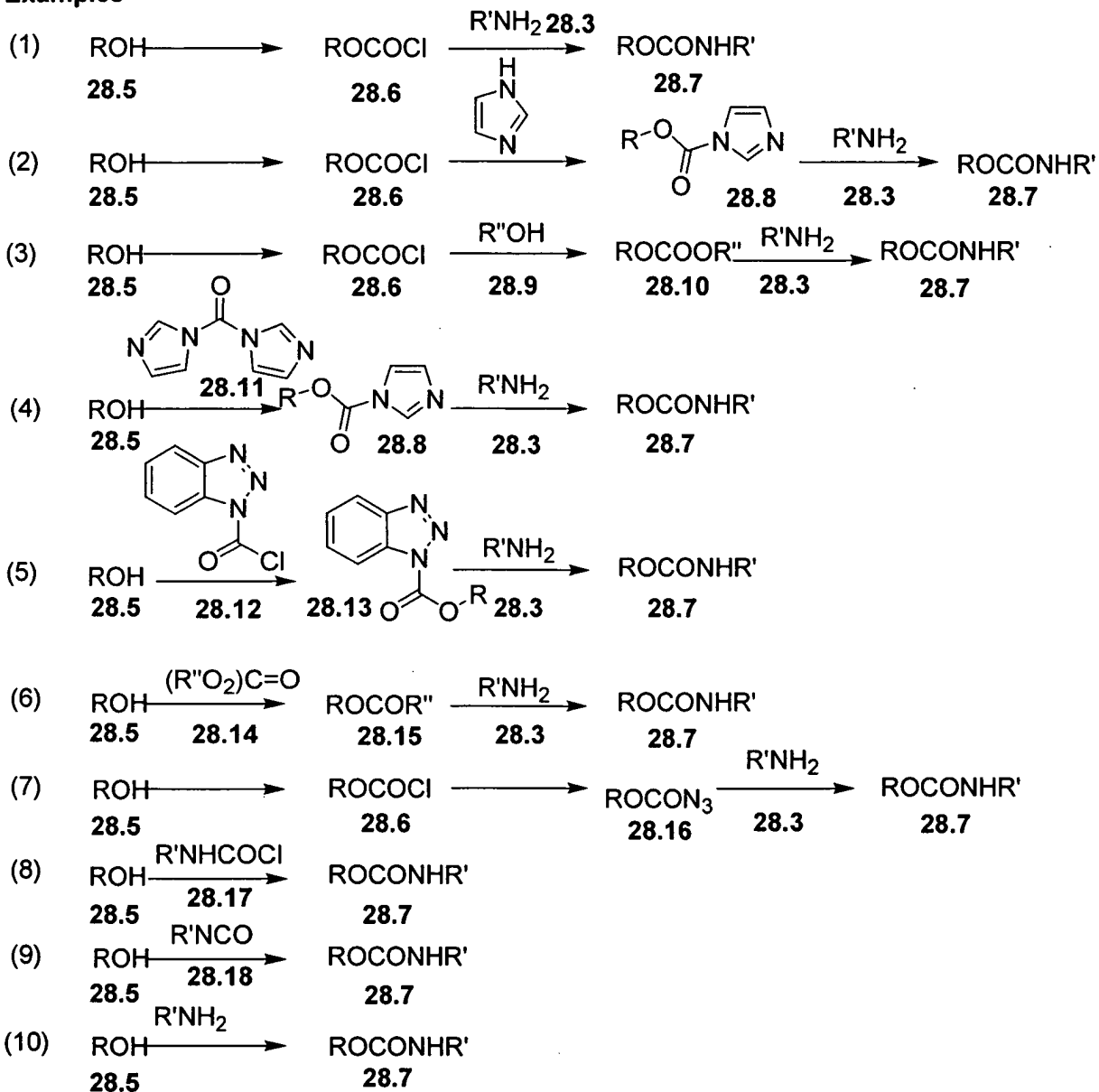
Scheme **28**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine R'NH<sub>2</sub>. In this procedure, which is described in *Chem. Lett.* 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **28.7**.

# Scheme 28

## General reaction



## Examples



**Preparation of phosphonate intermediates 6 and 7  
with phosphonate moieties incorporated into the group  $R^2\text{COOH}$  and  $R^3\text{COOH}$**

The chemical transformations described in Schemes 1-28 illustrate the preparation of compounds 1-5 in which the phosphonate ester moiety is attached to the thiazole substructure, (Schemes 1-3, 9-10, and 11-12), the phenylalanine moiety (Schemes 4-6), and the benzyl moiety (Schemes 7-8).

The various chemical methods employed for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds  $R^2\text{COOH}$  and  $R^3\text{COOH}$ , as defined in Charts 2a, 2b and 2c. The resultant phosphonate-containing analogs, designated as  $R^{2a}\text{COOH}$  and  $R^{3a}\text{COOH}$  can then, using the procedures described above, be employed in the preparation of the compounds 6 and 7. The procedures required for the introduction of the phosphonate-containing analogs  $R^{2a}\text{COOH}$  and  $R^{3a}\text{COOH}$  are the same as those described above (Schemes 4, 5, and 28) for the introduction of the  $R^2\text{CO}$  and  $R^3\text{CO}$  moieties.

**Indinavir-like phosphonate protease inhibitors (ILPPI)**

**Preparation of the intermediate phosphonate esters 1-24**

The structures of the intermediate phosphonate esters 1 to 22 and the structures of the component groups  $R^1$ ,  $R^4$ ,  $R^8$ ,  $R^9$ ,  $R^{11}$ , X and X' of this invention are shown in Charts 1 - 3. The structures of the  $R^2R^3\text{NH}$  components are shown in Chart 4; the structures of the amines components  $R^7\text{NHCH}(R^6)\text{CONHR}^4$  are shown as the structures A1 - A16 in Chart 4. The structures of the  $R^5\text{XCH}_2$  groups are shown in Chart 5, and those of the  $R^{10}\text{CO}$  components are illustrated in Chart 6. The structures of the  $R^7\text{NHCH}(R^6)\text{COOH}$  components are shown in Chart 10.

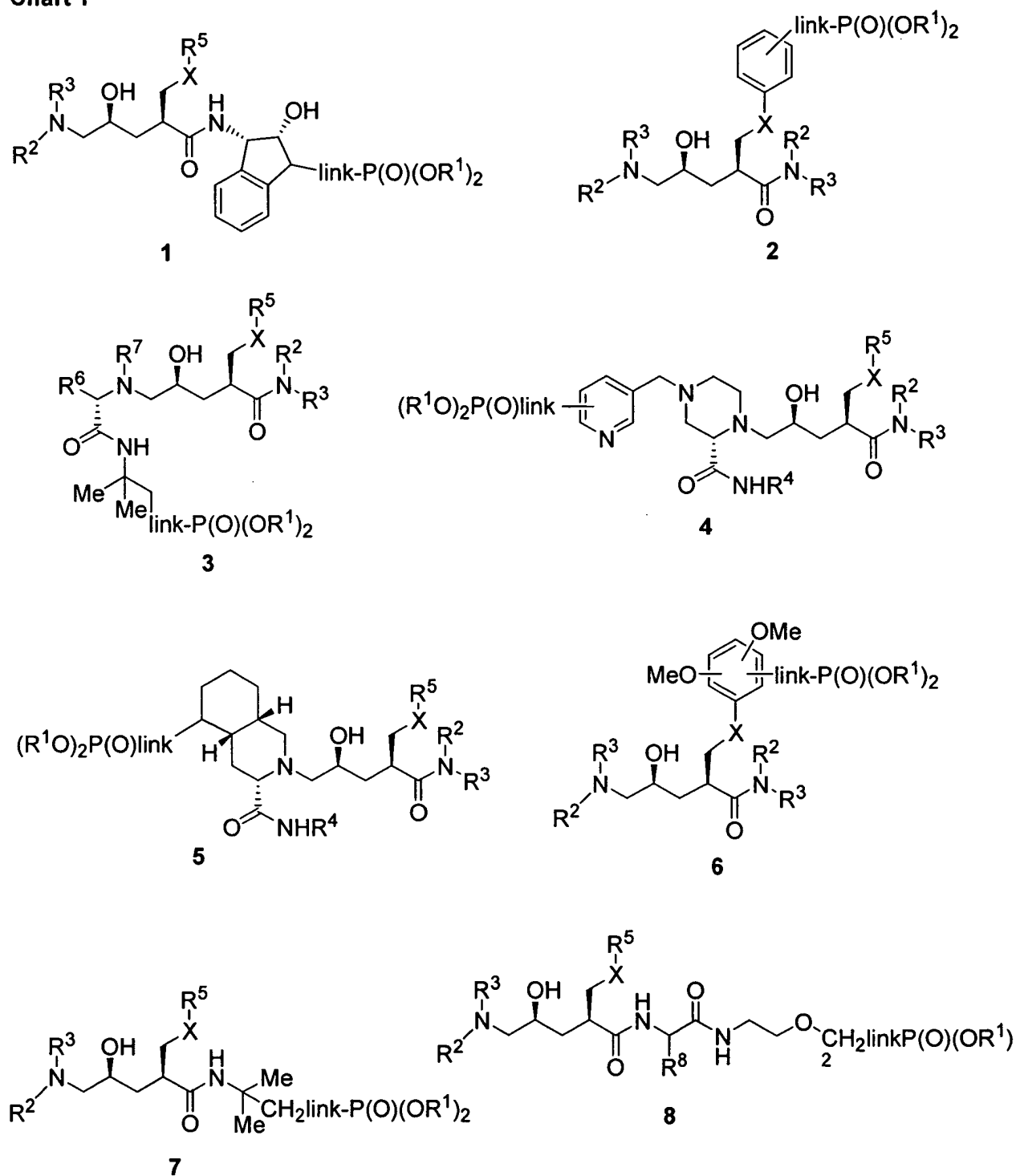
Specific stereoisomers of some of the structures are shown in Charts 1 - 10; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 24. Subsequent chemical modifications to the compounds 1 to 24, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds 1 to 24 incorporate a phosphonate moiety  $(R^1\text{O})_2\text{P}(\text{O})$  connected to the nucleus by means of a variable linking group, designated as "link" in the

attached structures. Charts 7, 8 and 9 illustrate examples of the linking groups present in the structures 1 – 24.

Schemes 1 - 207 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1 - 22, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 23 and 24, in which a phosphonate moiety is incorporated into one of the groups  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^{10}$  or  $R^{11}$  is also described below. In compounds 2, 6, 23 and 24 where two groups are the same Chart 4 it is noted that these groups may be independent or identical.

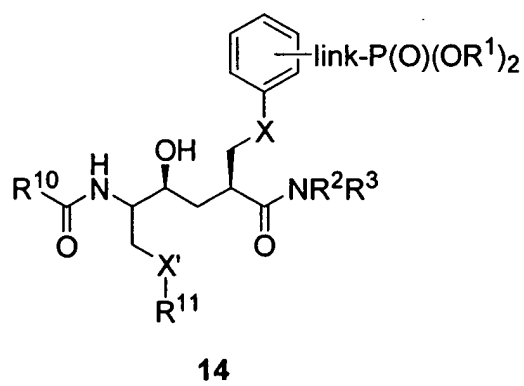
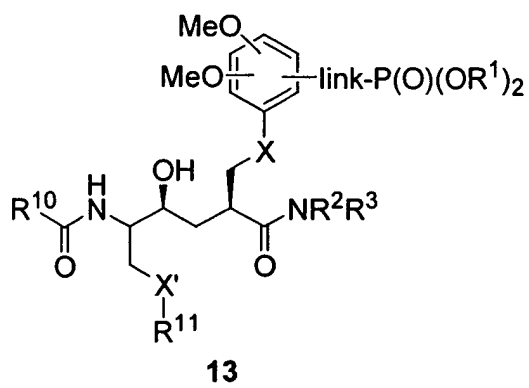
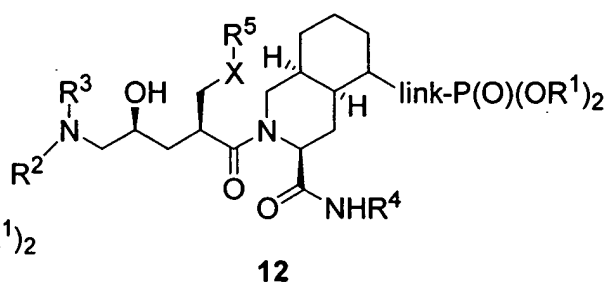
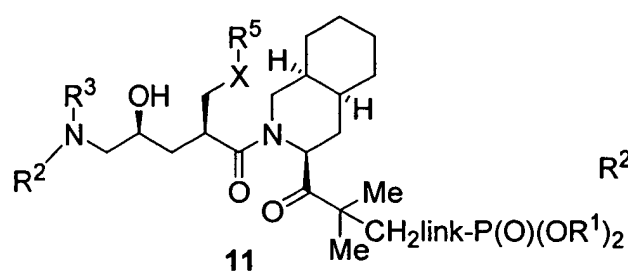
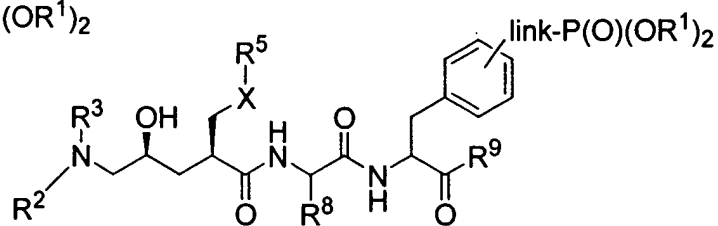
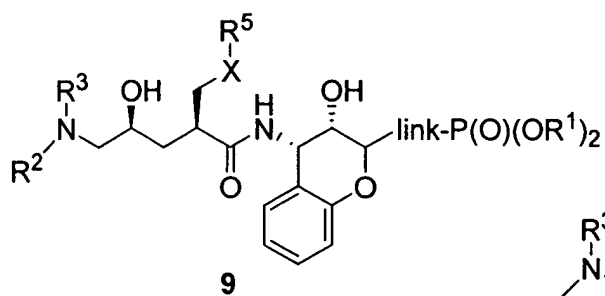
**Chart 1**

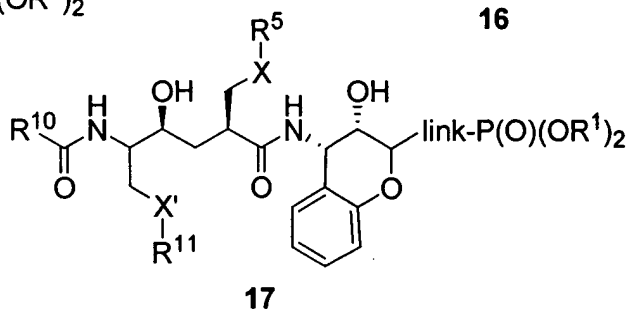
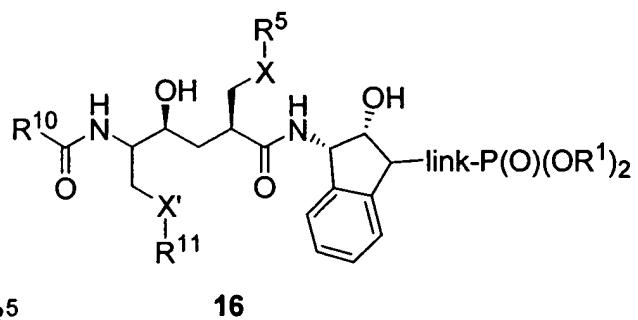
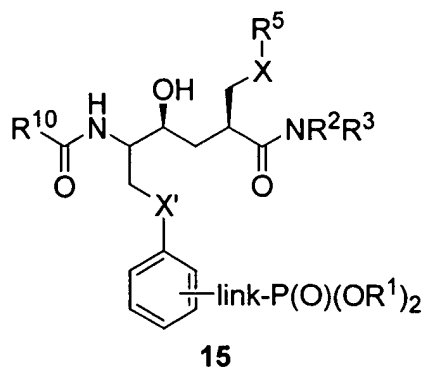


$\text{R}^1$  = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

$\text{R}^4$  =  $\text{CH}(\text{CH}_3)_3$ ;  $\text{CH}_2\text{CF}_3$ ;  $\text{CH}_2\text{C}_6\text{H}_4(\text{CH}_3)-2$ ;  $\text{CH}_2\text{C}_6\text{H}_3(\text{CH}_3)_2$  2,6

Chart 2





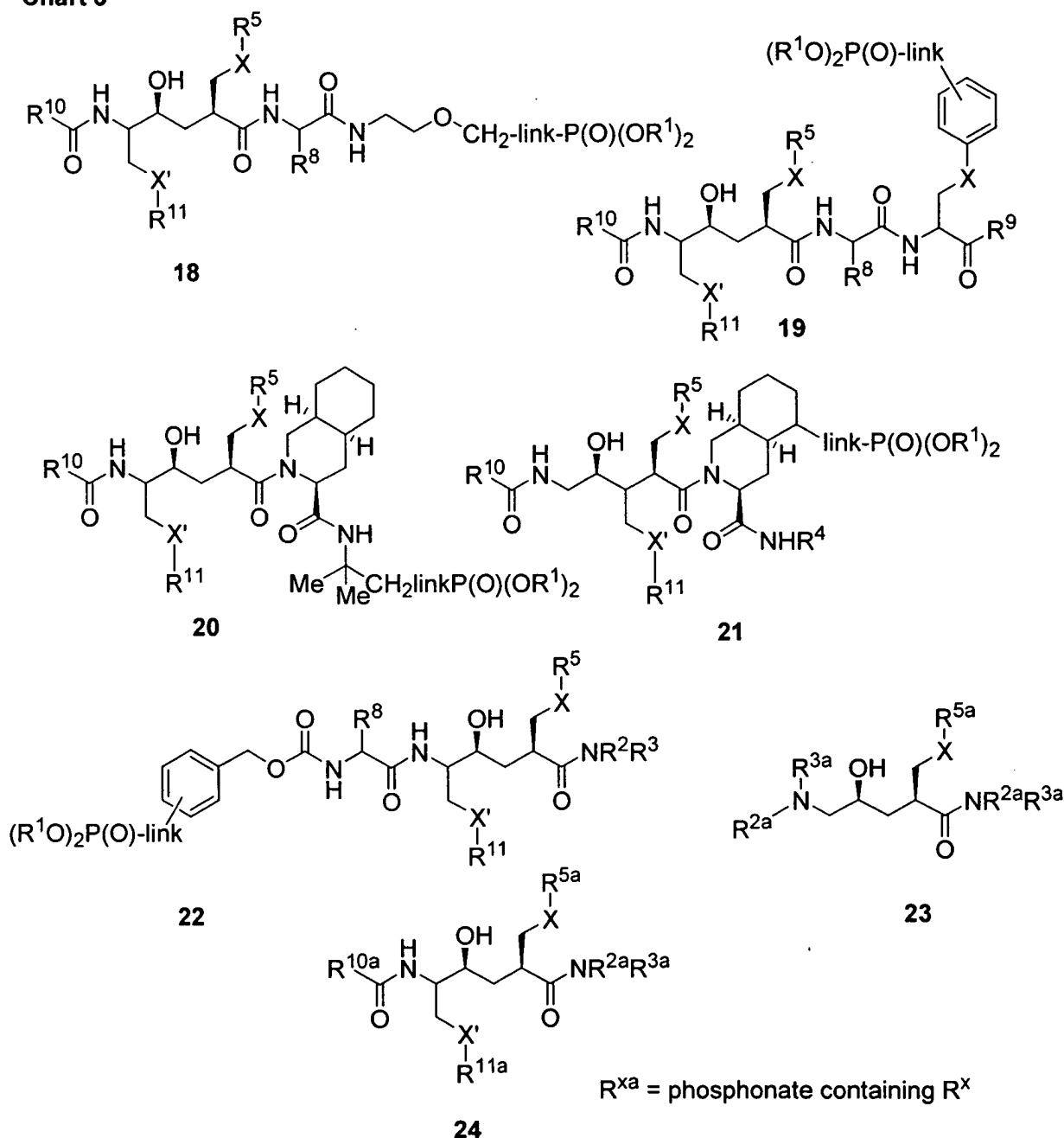
$R^{11}$  = phenyl, alkyl

$R^1$  = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

$R^4$  =  $\text{CH}(\text{CH}_3)_3$ ;  $\text{CH}_2\text{CF}_3$ ;  $\text{CH}_2\text{C}_6\text{H}_4(\text{CH}_3)_2$ ;  $\text{CH}_2\text{C}_6\text{H}_3(\text{CH}_3)_2$  2,6

$R^9$  = morpholino or methoxy

Chart 3



$R^1$  = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

$R^4$  =  $C(CH_3)_3$ ;  $CH_2CF_3$ ;  $CH_2C_6H_4(CH_3)_2$  2,6

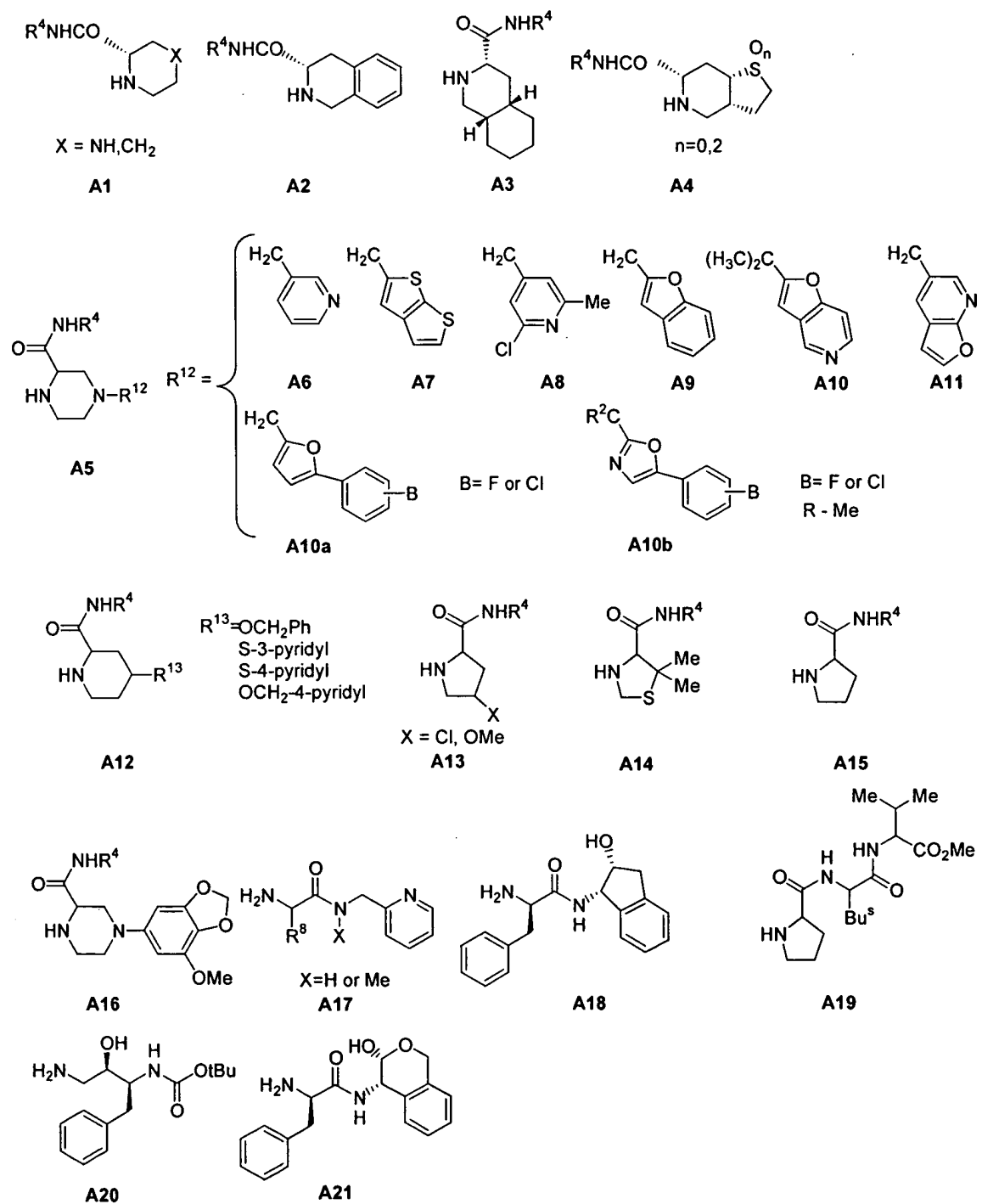
$R^8$  = alkyl,  $CH_2SO_2CH_3$ ,  $C(CH_3)_2SO_2CH_3$ ,  $CH_2CONH_2$ ,  $CH_2SCH_3$ , imidaz-4-ylmethyl,  $CH_2NHAc$ ,  $CH_2NHCOCF_3$

$R^9$  = morpholino; alkoxy.

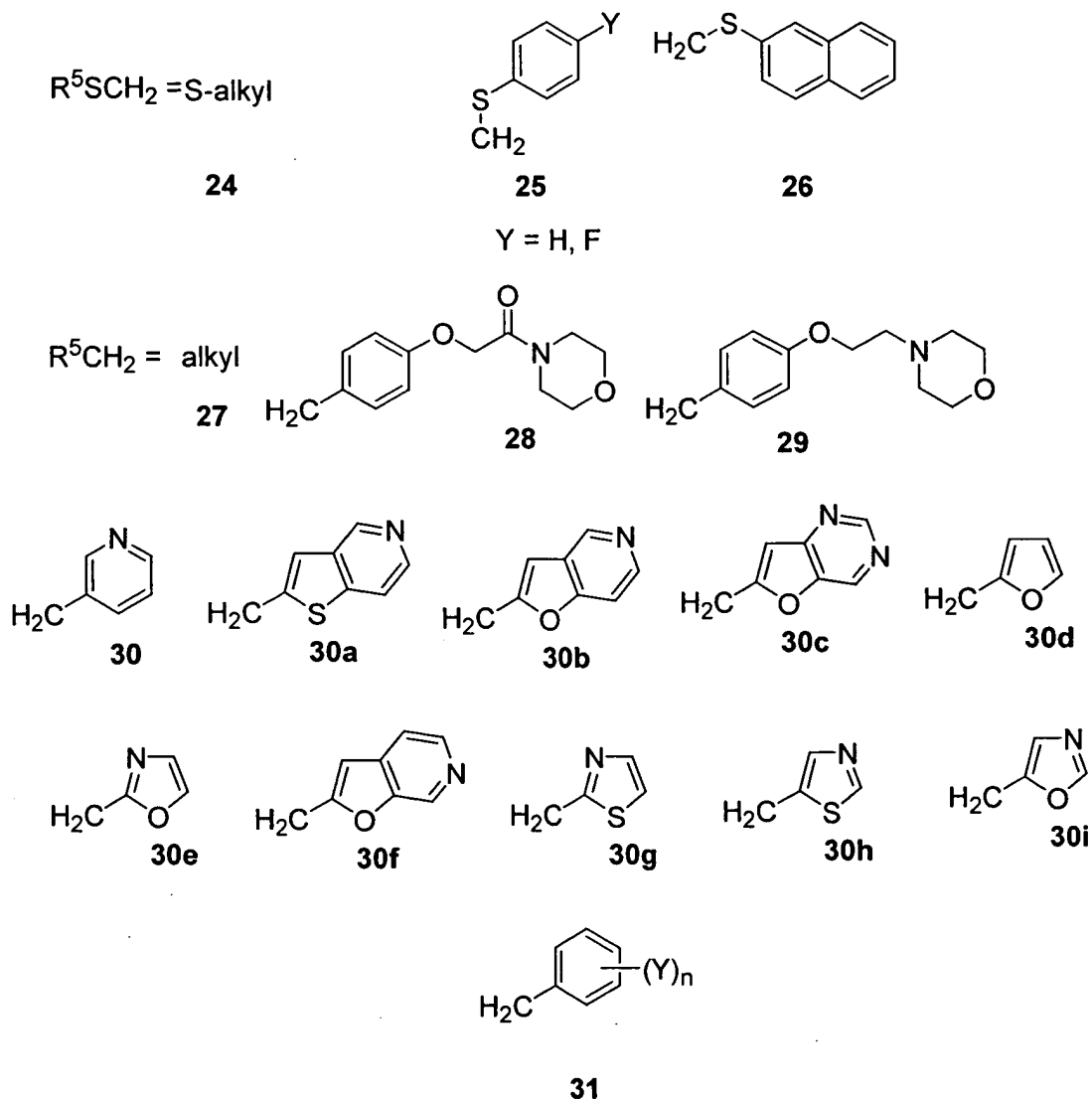
$R^{11}$  = phenyl, alkyl

X, X' = S, direct bond

Chart 4 Structures of the R<sup>2</sup>R<sup>3</sup>NH components

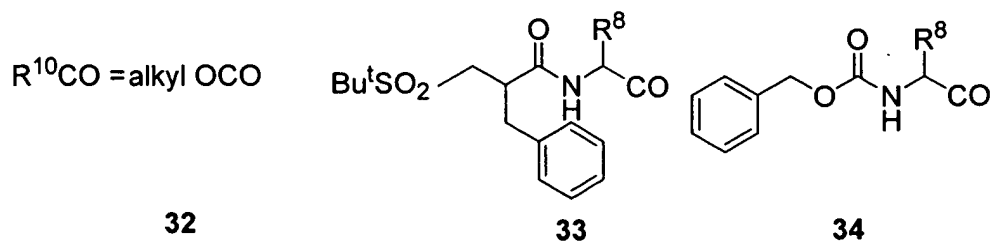


**Chart 5. Structures of the R<sup>5</sup>XCH<sub>2</sub> groups.**



Y = H, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, MeO, (MeO)<sub>2</sub>, (MeO)<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>OH, OH, Ha, CN, Ph, OCH<sub>2</sub>O, OCH<sub>2</sub>Ph

**Chart 6. Structures of the R<sup>10</sup>CO components**



**Chart 7. Examples of linking groups**

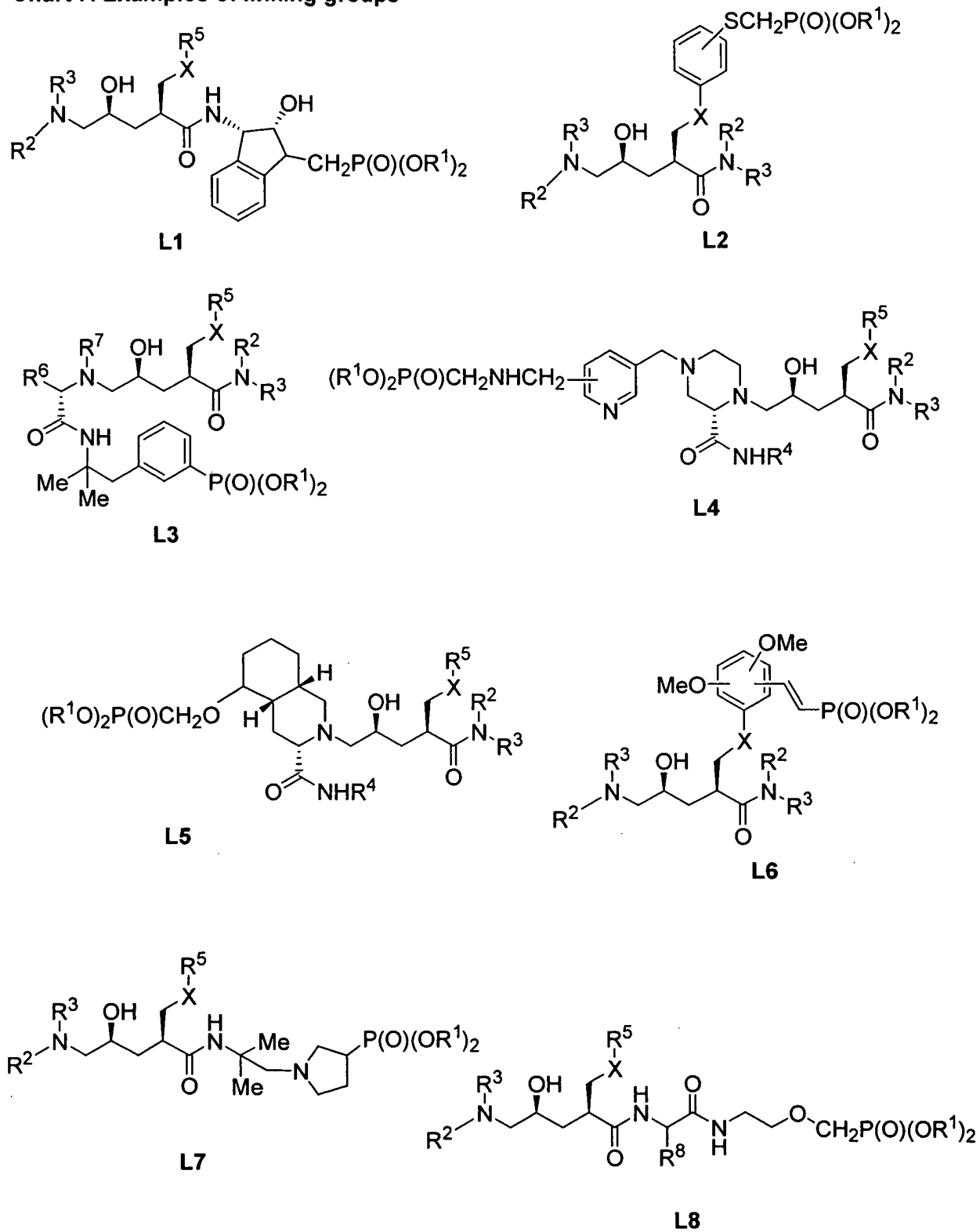
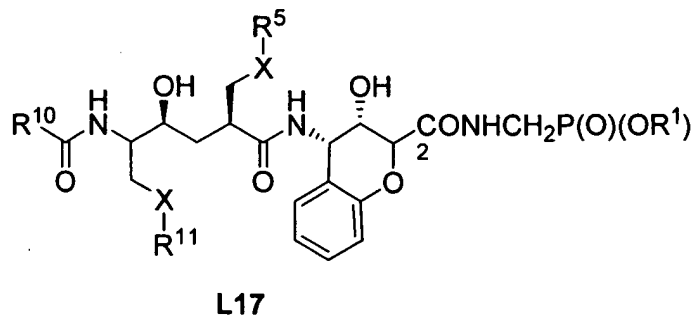
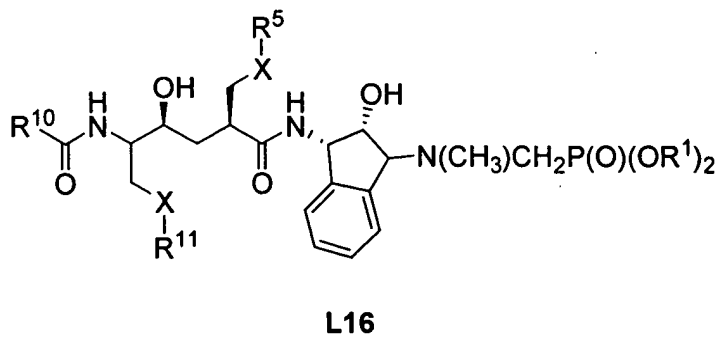
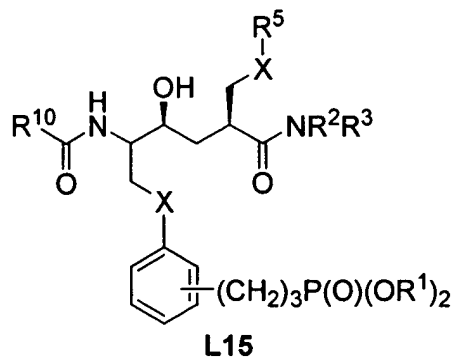
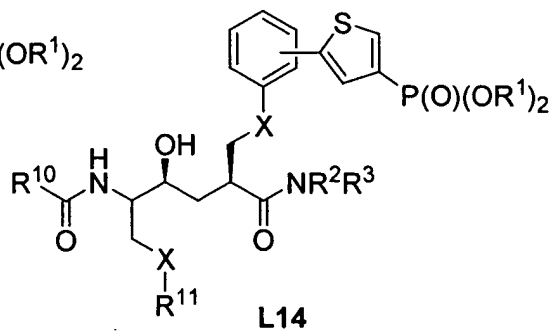
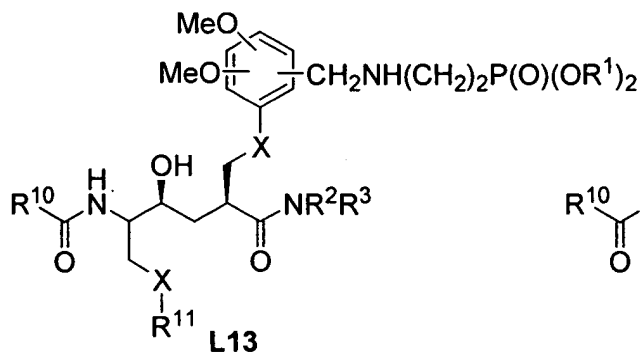
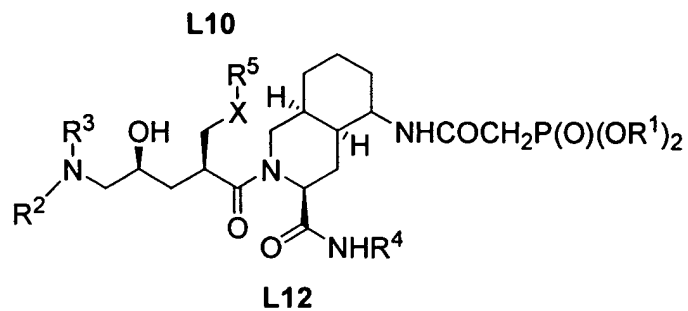
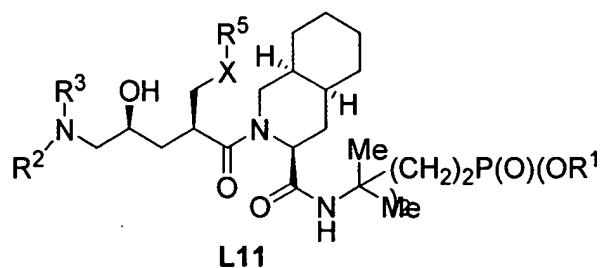
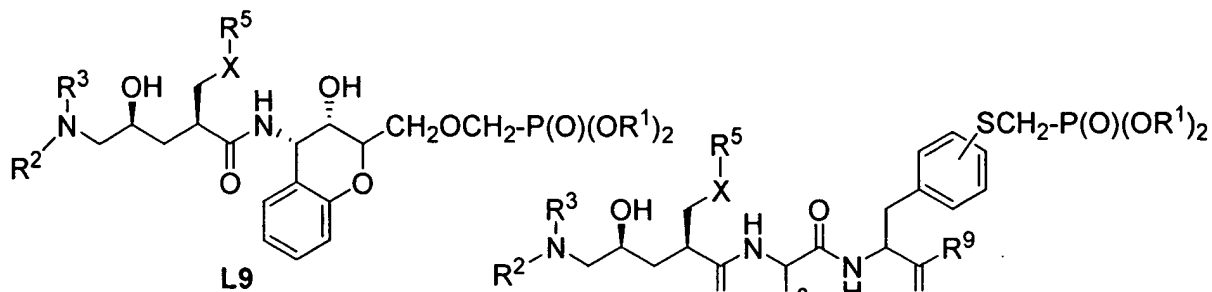
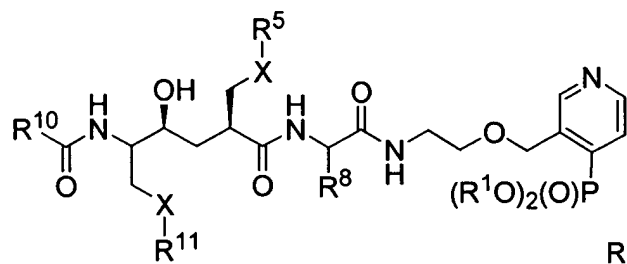


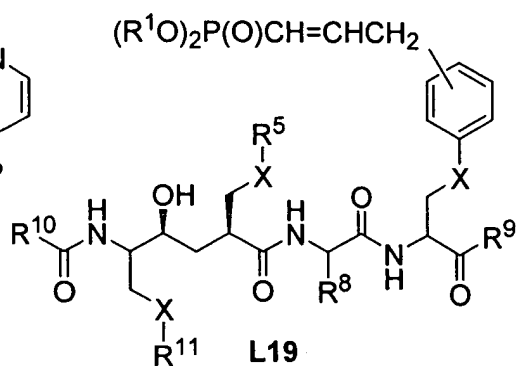
Chart 8. Examples of linking groups



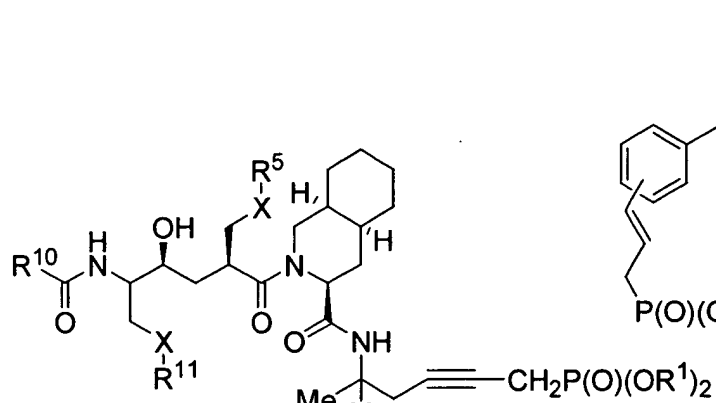
**Chart 9. Examples of linking groups**



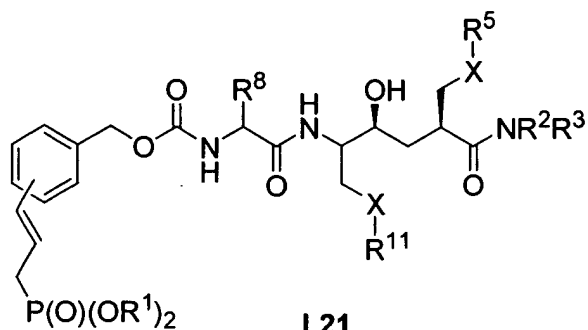
**L18**



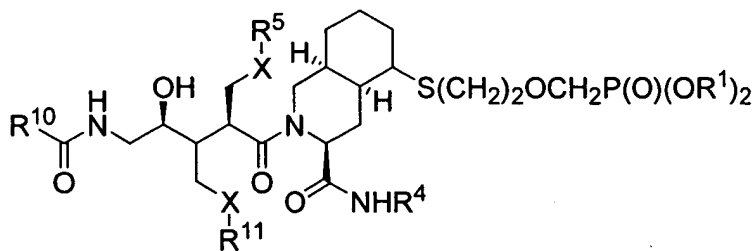
**L19**



**L20**

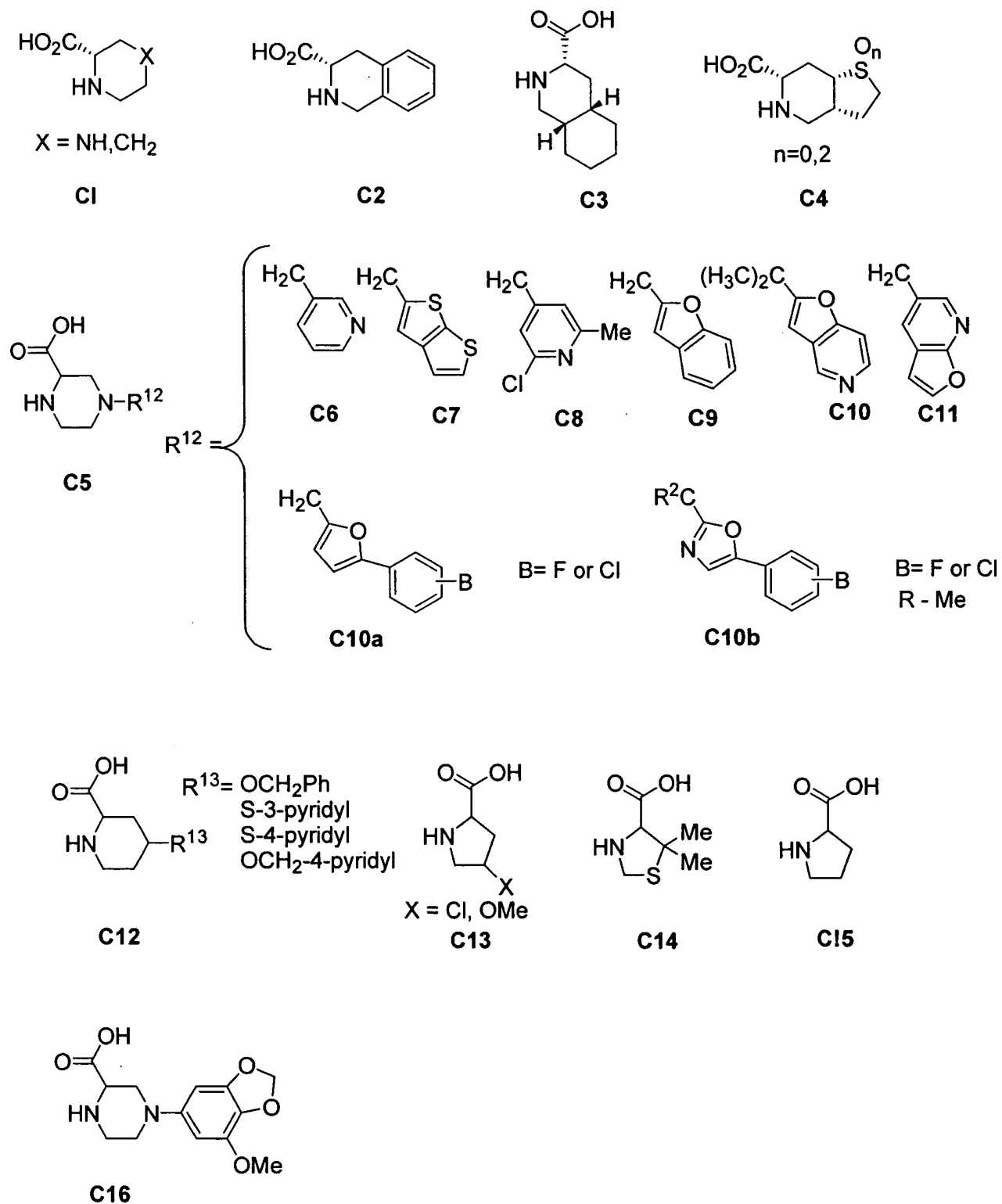


**L21**



**L22**

Chart 10. Structures of the  $R^7NHCH(R^6)COOH$  components



## Protection of reactive substituents

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

## Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

The intermediate phosphonate esters 1, in which the group A is attached to the aminoindanol moiety, are prepared as shown in Schemes 1 and 2.

In this procedure, the propionic acid 1.1, or an activated derivative thereof, is reacted with an aminoindanol derivative 1.2, in which the substituent A is either the group link- $P(O)(OR^1)_2$  or a precursor such as [OH], [SH], [NH], Br, to afford the amide 1.3. The preparation of the aminoindanol derivatives 1.2 is described in Schemes 133 - 137.

The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid 1.1 is reacted with an equimolar amount of the amine 1.2 in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, in an aprotic solvent such as, for example, tetrahydrofuran, at about ambient temperature, so as to afford the amide product 1.3. The amide is then reacted with 2-(S)glycidyl tosylate 1.4, or an equivalent thereof, such as,

for example, 2-(S) glycidyl p-nitrobenzenesulfonate, as described in Tet Lett., 35, 673, 1994. To effect the reaction, the amide **1.3** is first converted into the  $\alpha$ -anion, by treatment with a strong base, such as, for example, sodium hydride, potassium tert. butoxide and the like. The anion is then reacted with the epoxide **1.4**, or an equivalent, as described above, in an inert solvent such as, for example, dimethylformamide, dioxan and the like. The reaction is conducted at a temperature of from 0°C to -100°C to yield the alkylated product **1.5**.

Preferably, equimolar amounts of the amide **1.3** and the epoxide **1.4** are dissolved in tetrahydrofuran at about -50°C, and a slight excess of lithium hexamethyldisilylazide is added, as described in WO 9612492 and *Tetrahedron Lett.*, 35, 673, 1994. The temperature is raised to about -25°C to effect stereoselective alkylation and conversion to the epoxide **1.5**.

The thus-obtained epoxide **1.5** is then subjected to a regiospecific ring-opening reaction with the amine **1.6** to yield the hydroxyamine **1.7**. The preparation of hydroxyamines by the reaction between an amine and an epoxide is described, for example, in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1968, p. 357. The amine and the epoxide are reacted together in a polar organic solvent such as, for example, dimethylformamide or an alcohol, to effect the ring-opening reaction.

Preferably, equimolar amounts of the amine **1.6** and the epoxide **1.5** are heated in isopropanol at reflux for about 24 hours, to prepare the hydroxyamine product **1.7**, for example as described in WO 9628439 and *Tetrahedron Lett.*, 35, 673, 1994.

The hydroxyamine product **1.7** is then deprotected to remove the acetonide group and produce the compound **1.8** in which A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Acetonide protecting groups are removed by treatment with an acid, for example acetic acid or dilute hydrochloric acid, optionally in the presence of water and a water-miscible organic solvent such as, for example, tetrahydrofuran or an alcohol.

Preferably, the acetonide protecting group is removed by treatment of the acetonide **1.7** with 6N hydrochloric acid in isopropanol at ambient temperature, as described in WO 9612492, to afford the indanol **1.8**.

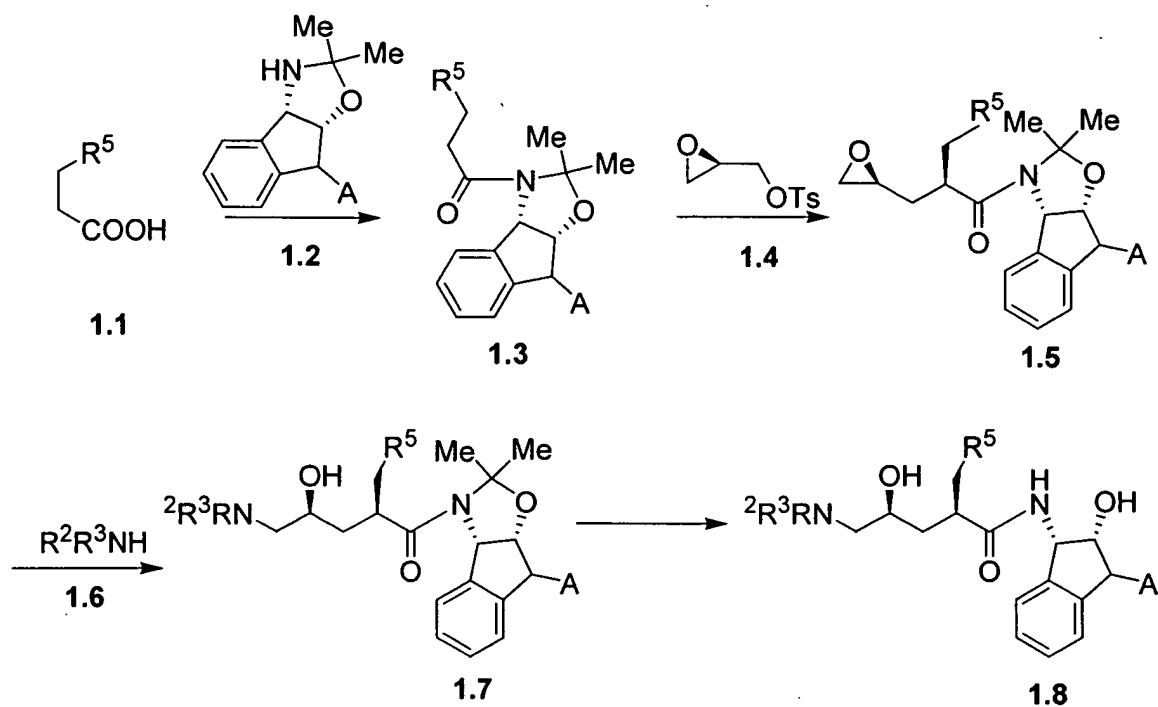
The reactions shown in Scheme 1 illustrate the preparation of the compounds **1.8** in which A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 2 depicts the conversion of the compounds **1.8** in which A is [OH], [SH], [NH], Br, into the compounds **1** in which A is the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>. In this procedure, the compounds **1.7**

are converted, using the procedures described below, Schemes 133 - 197, into the compounds 2.1. Deprotection, by removal of the acetonide protecting group, as described above, then affords the intermediate phosphonate esters **1** in which X is a direct bond.

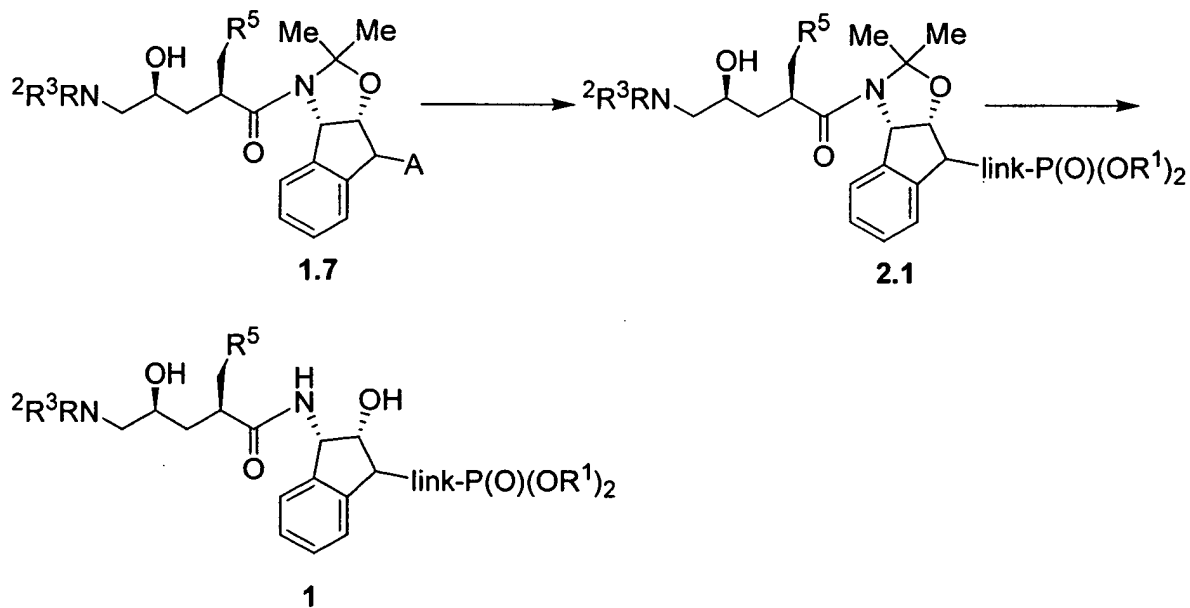
In the preceding and following schemes, the conversion of various substituents into the group  $\text{link-P(O)(OR}^1\text{)}_2$  can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group  $\text{link-P(O)(OR}^1\text{)}_2$ .

In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 199).

### Scheme 1



### Scheme 2



### Preparation of the phosphonate ester intermediates **1** in which X is sulfur

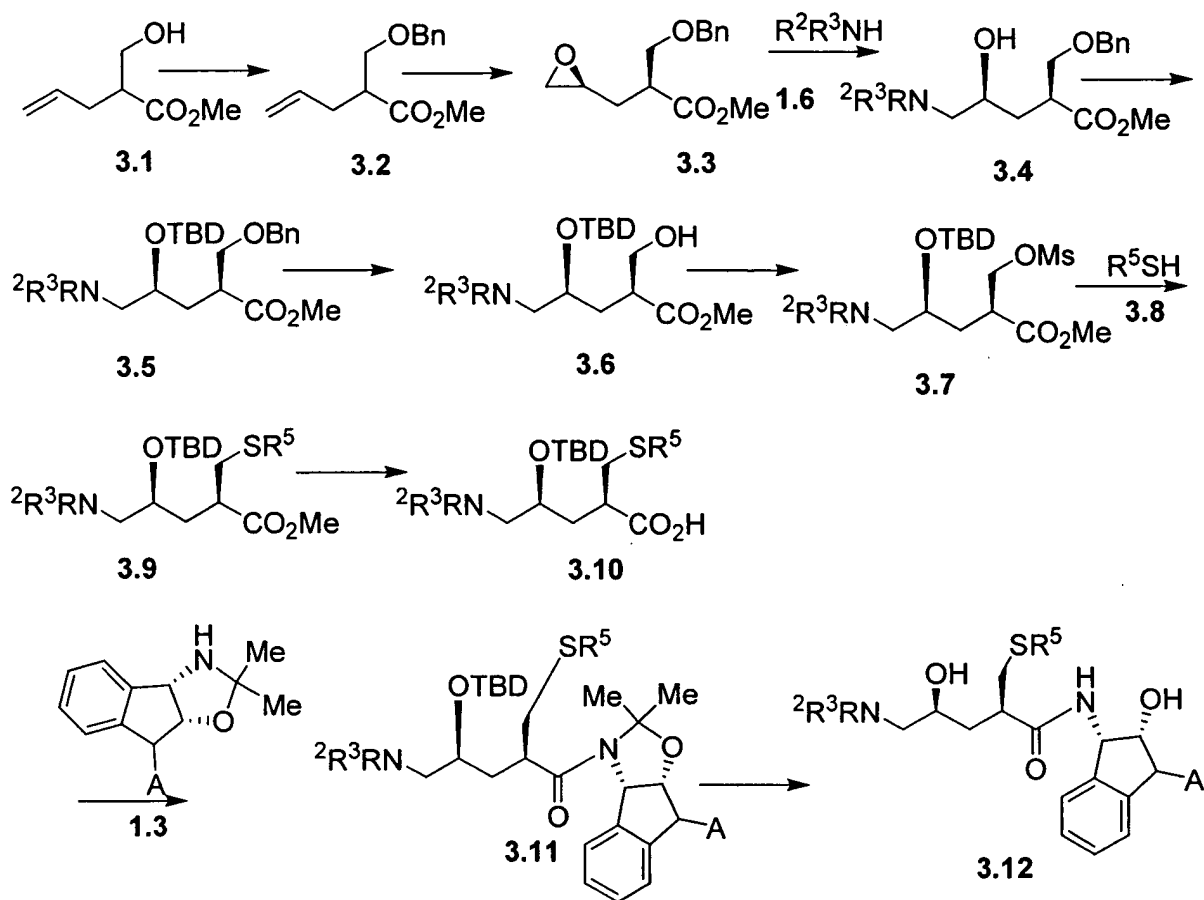
Schemes 3 and 4 illustrate the preparation of the phosphonate esters **1** in which X is sulfur. As shown in Scheme 3, methyl 2-allyl-3-hydroxypropionate **3.1**, prepared as described in *Tetrahedron Lett.*, 1973, 2429, is converted into the benzyl ether **3.2**. The conversion of alcohols

into benzyl ethers is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 47. The reaction is effected by treatment of the carbinol with a benzyl halide, in the presence of a base such as potassium hydroxide, silver oxide, sodium hydride and the like, in an organic or aqueous organic solvent, optionally in the presence of a phase transfer catalyst. Preferably, the carbinol **3.1** is reacted with benzyl bromide and silver oxide in dimethylformamide at ambient temperature for 48 hours, to afford the product **3.2**. The benzyl ether is then subjected to an epoxidation reaction to produce the epoxide **3.3**. The conversion of olefins into epoxides is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 456. The reaction is performed by the use of a peracid such as peracetic acid, m-chloroperbenzoic acid or monoperphthalic acid, optionally in the presence of a base such as potassium carbonate or sodium bicarbonate, or by the use of tert. butyl hydroperoxide, optionally in the presence of a chiral auxiliary such as diethyl tartrate. Preferably, equimolar amounts of the olefin and m-chloroperbenzoic acid are reacted in dichloromethane in the presence of sodium bicarbonate, as described in *Tetrahedron Lett.*, 849, 1965, to afford the epoxide **3.3**. This compound is then reacted with the amine **1.6** to yield the hydroxyamine **3.4**. The reaction is performed as described above for the preparation of the hydroxyamine **1.7**. The hydroxyl substituent is then protected by conversion to the silyl ether **3.5**, in which OTBD is tert. butyldimethylsilyloxy. The preparation of silyl ethers is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 77. The reaction is effected by treatment of the carbinol with tert. butylchlorodimethylsilane and a base such as imidazole, dimethylaminopyridine or 2,6-lutidine, in an organic solvent such as dichloromethane or dimethylformamide. Preferably, equimolar amounts of the carbinol, tert. butylchlorodimethylsilane and imidazole are reacted in dimethylformamide at ambient temperature to give the silyl ether **3.5**. The benzyl ether is then removed to afford the carbinol **3.6**. The removal of benzyl protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 49. The conversion is effected by means of catalytic hydrogenation over a palladium catalyst, with hydrogen or a hydrogen transfer agent, or by electrolytic reduction, by treatment with trimethylsilyl iodide, or by the use of a Lewis acid such as boron trifluoride or stannic chloride, or by oxidation with ferric chloride or ruthenium dioxide. Preferably, the benzyl ether is removed by reaction of the substrate with 5% palladium on carbon catalyst and

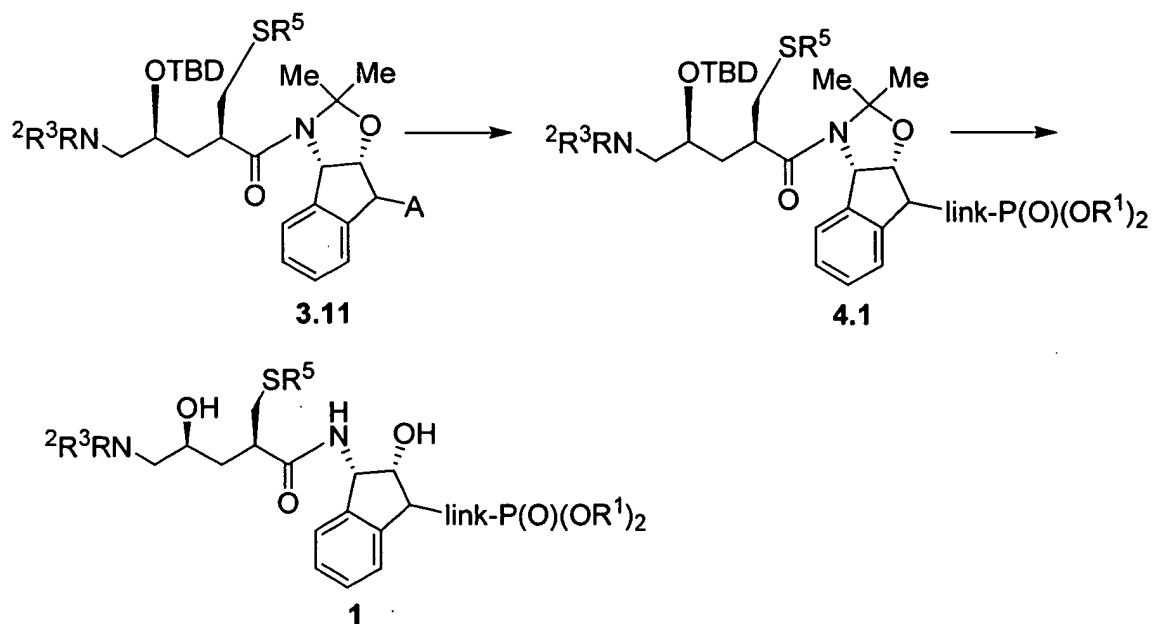
ammonium formate in refluxing methanol, as described in *Synthesis*, 76, 1985. The resultant carbinol **3.6** is then converted into the mesylate ester **3.7** by reaction with one molar equivalent of methanesulfonyl chloride or anhydride, in an organic solvent such as dichloromethane, and in the presence of a base such as dimethylaminopyridine or diisopropylethylamine. The product **3.7** is then reacted with the thiol  $R^5SH$ , to prepare the thioether **3.9**. The preparation of thioethers by alkylation of thiols is described in *Synthetic Organic Chemistry*, by R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reaction is effected by treatment of the thiol with a base such as sodium hydroxide, potassium carbonate or diazabicyclononene, in a solvent such as ethanol or dioxan, in the presence of the mesylate **3.7**, to afford the product **3.9**. The methyl ester moiety present in the latter compound is then hydrolyzed to give the carboxylic acid **3.10**. The transformation is effected hydrolytically, for example by the use of an alkali metal hydroxide in an aqueous organic solvent, or enzymically, for example by the use of porcine liver esterase, as described in *J. Am. Chem. Soc.*, 104, 7294, 1982. Preferably, the ester group is hydrolyzed by treatment of the ester **3.9** with one molar equivalent of lithium hydroxide in aqueous methanol at ambient temperature, to give the carboxylic acid **3.10**. The latter compound is then reacted, as described above, with the aminoindanol acetonide **1.3** to give the amide **3.11**. Removal of the acetonide group, as described above, with concomitant desilylation, then affords the hydroxyamide **3.12**.

The reactions shown in Scheme 3 illustrate the preparation of the compounds **3.12** in which A is either the group  $\text{link-P(O)(OR}^1\text{)}_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 4 depicts the conversion of the compounds **3.11** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **1** in which X is sulfur. In this procedure, the compounds **3.11** are converted, using the procedures described below, Schemes 133 - 197, into the compounds **4.1**. Deprotection, by removal of the acetonide protecting group, as described above, then affords the intermediate phosphonate esters **1** in which X is sulfur.

**Scheme 3**



**Scheme 4**

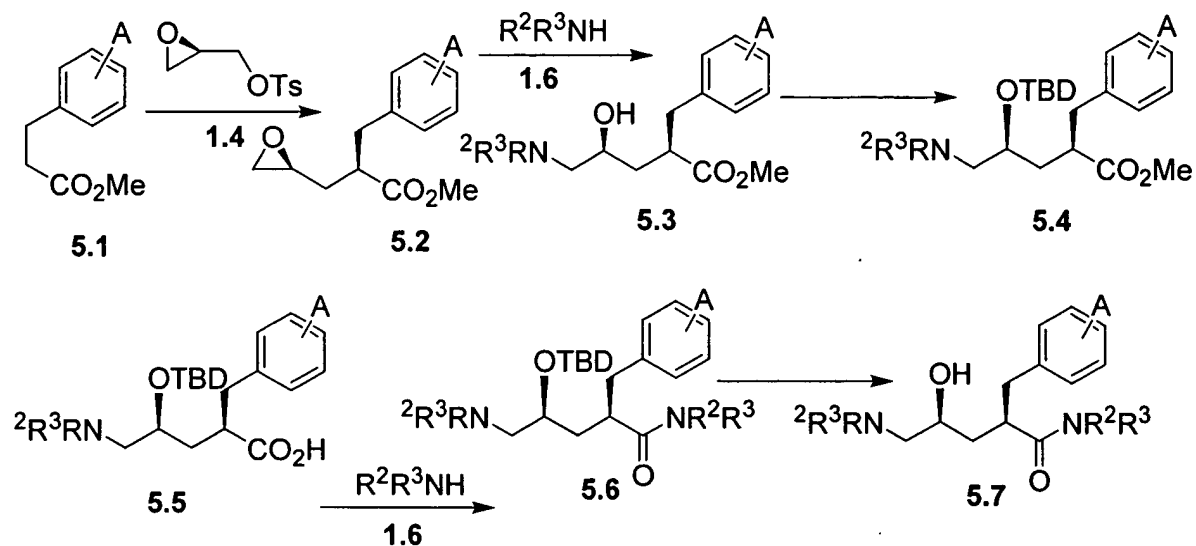


### Preparation of the phosphonate ester intermediates 2 in which X is a direct bond

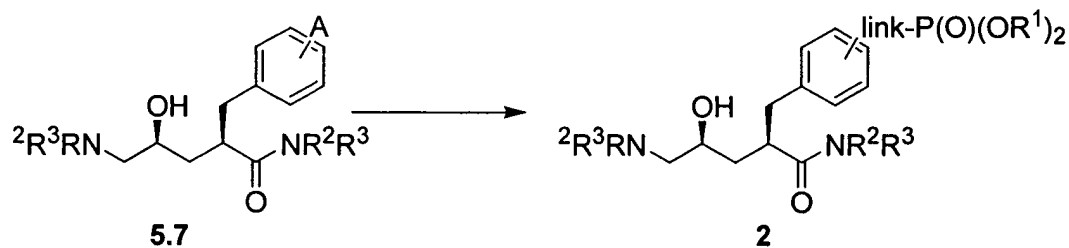
Schemes 5 and 6 illustrate the preparation of the phosphonate esters 2 in which X is a direct bond. As shown in Scheme 5, the substituted phenyl propionic ester 5.1, in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br, is reacted with the glycidyl tosylate 1.4 to afford the alkylated product 5.2. The preparation of the phenylpropionic esters 5.1 is described below, (Schemes 138 - 143). The reaction is performed as described above for the preparation of the oxirane 1.5. The product 5.2 is then reacted with the amine R<sup>2</sup>R<sup>3</sup>NH (1.6) to yield the hydroxyamine 5.3. The reaction is performed as described above for the preparation of the hydroxyamine 1.7. The secondary hydroxy group is then protected, for example by conversion to the tert. butyldimethyl silyl ether 5.4, using the conditions described above for the preparation of the silyl ether 3.5. The methyl ester is then hydrolyzed to produce the carboxylic acid 5.5, using the conditions described above for the hydrolysis of the methyl ester 3.9. The carboxylic acid is then coupled with the amine 1.6 to give the amide 5.6. The reaction is effected under the conditions described above for the preparation of the amide 1.3. The product is desilylated, for example by treatment with 1M tetrabutyl ammonium fluoride in tetrahydrofuran, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972, to give the carbinol 5.7.

The reactions shown in Scheme 5 illustrate the preparation of the compounds 5.7 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br, as described herein. Scheme 6 depicts the conversion of the compounds 5.7 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 2 in which X is a direct bond. In this procedure, the compounds 5.7 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 2.

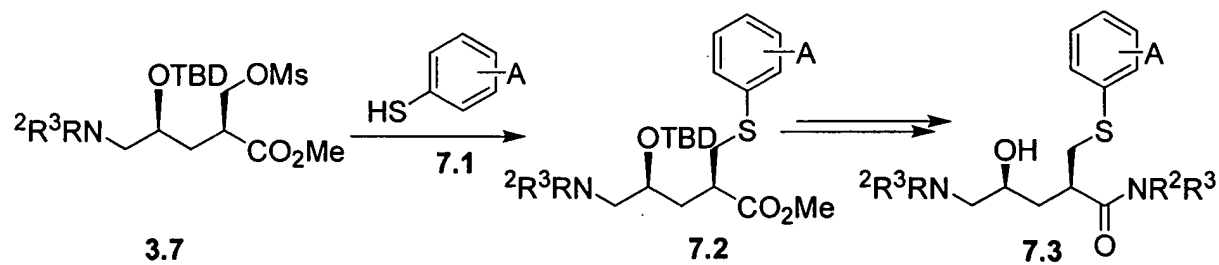
# **Scheme 5**



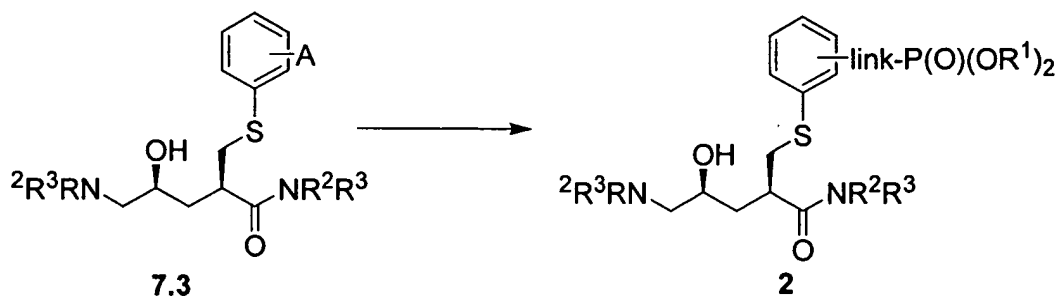
# **Scheme 6**



# **Scheme 7**



# **Scheme 8**



### **Preparation of the phosphonate ester intermediates 2 in which X is sulfur**

Schemes 7 and 8 illustrate the preparation of the phosphonate esters 2 in which X is sulfur. As shown in Scheme 7, the mesylate 3.7 is reacted with the thiophenol 7.1, in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br, to afford the thioether 7.2. The reaction is performed under the same conditions as described above for the preparation of the thioether 3.9. The preparation of the thiophenols 7.2 is described in Schemes 144 - 153. The product 7.2 is then transformed, using the sequence of reactions described above for the conversion of the ester 5.4 into the aminoamide 5.7, into the aminoamide 7.3.

The reactions shown in Scheme 7 illustrate the preparation of the compounds 7.3 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 8 depicts the conversion of the compounds 7.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 2 in which X is sulfur. In this procedure, the compounds 7.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 2.

### **Preparation of the phosphonate ester intermediates 3 in which X is a direct bond**

Schemes 9 and 10 illustrate the preparation of the phosphonate esters 3 in which X is a direct bond. As shown in Scheme 9, the methyl ester 9.1 is reacted, as described above, (Scheme 1) with the epoxide 1.4 to afford the alkylated ester 9.2. The product is then reacted with the amine 9.3, in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor, to yield the hydroxyamine 9.4. The preparation of the tert. butylamine derivatives 9.3 is described below, (Schemes 154 - 158). The hydroxyamine is then transformed, using the sequence of reactions described above for the conversion of the aminoester 5.3 into the aminoamide 5.7, into the aminoamide 9.5.

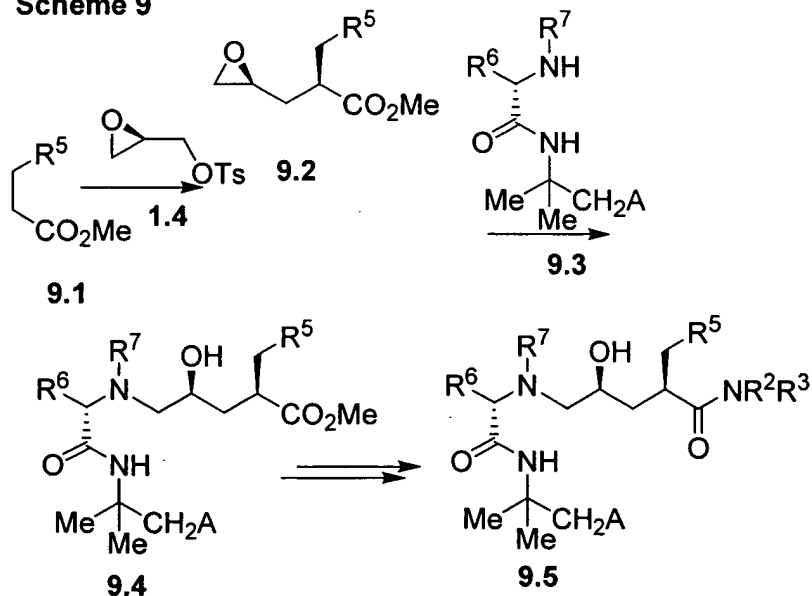
The reactions shown in Scheme 9 illustrate the preparation of the compounds 9.5 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 10 depicts the conversion of the compounds 9.5 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 3 in which X is a direct bond. In this procedure, the compounds 9.5 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 3.

### Preparation of the phosphonate ester intermediates 3 in which X is sulfur

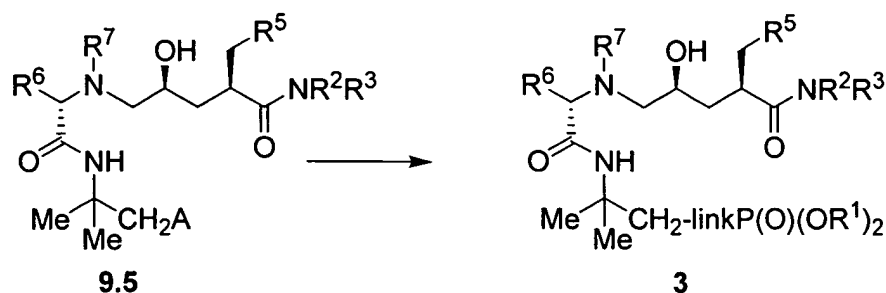
Schemes 11 and 12 illustrate the preparation of the phosphonate esters 3 in which X is sulfur. As shown in Scheme 11, the benzyl-protected oxirane 3.3 is reacted, as described above, with the substituted tert. butylamine 9.3 to afford the hydroxyamine 11.1. The product is then converted, using the sequence of reactions shown in Scheme 5 for the conversion of the hydroxyamine 5.3 into the aminoamide 5.7, into the aminoamide 11.2.

The reactions shown in Scheme 11 illustrate the preparation of the compounds 11.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 12 depicts the conversion of the compounds 11.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 3 in which X is sulfur. In this procedure, the compounds 11.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 3.

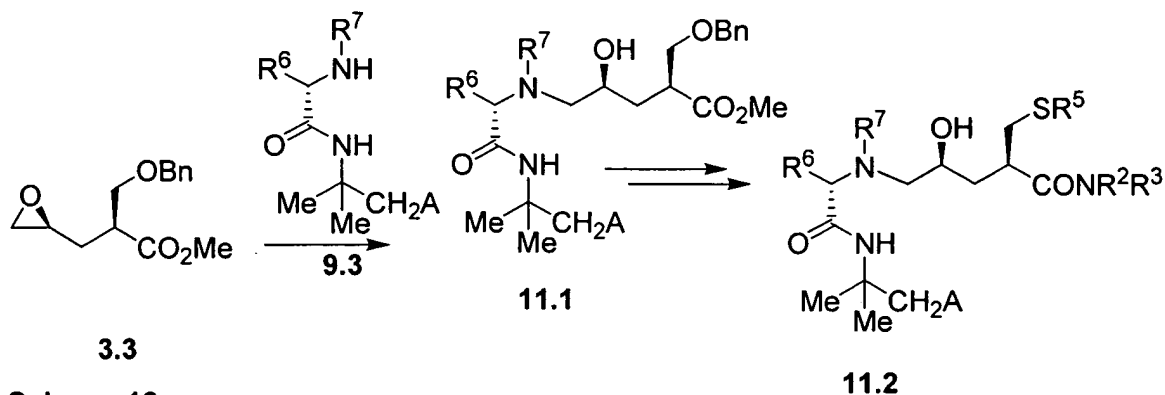
Scheme 9



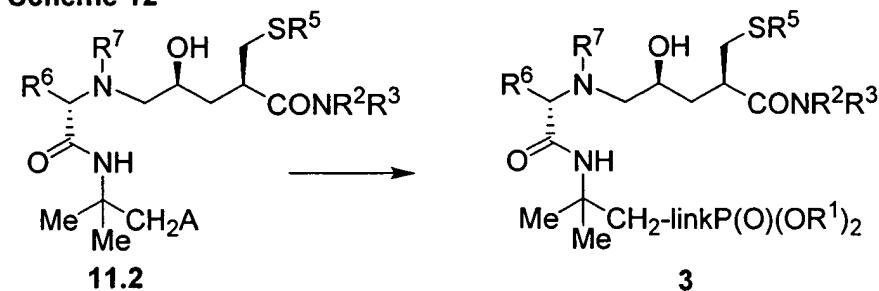
### Scheme 10



### Scheme 11



### Scheme 12



### Preparation of the phosphonate ester intermediates 4 in which X is a direct bond

Schemes 13 and 14 illustrate the preparation of the phosphonate esters 4 in which X is a direct bond. As shown in Scheme 13, the oxirane 9.2 is reacted, as described in Scheme 1, with the pyridyl piperazine derivative 13.1 to produce the hydroxyamine 13.2. The preparation of the pyridyl piperazine derivatives 13.1 is described in Schemes 159 – 164. The product is then transformed, as described previously, (Scheme 5) into the amide 13.3.

The reactions shown in Scheme 13 illustrate the preparation of the compounds 13.3 in which the substituent A is either the group  $\text{link-P(O)(OR}^1\text{)}_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 12 depicts the conversion of the compounds 13.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 4 in which X is a direct bond. In this procedure, the

compounds **13.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **4**.

#### **Preparation of the phosphonate ester intermediates **4** in which X is sulfur**

Schemes **15** and **16** illustrate the preparation of the phosphonate esters **4** in which X is sulfur. As shown in Scheme **15**, the benzyl-protected oxirane **3.3** is reacted, as described above, with the pyridyl piperazine derivative **13.1** to afford the hydroxyamine **15.1**. The product is then converted, as described above (Scheme **5**) into the aminoamide **15.2**.

The reactions shown in Scheme **15** illustrate the preparation of the compounds **15.2** in which the substituent A is either the group  $\text{link-P(O)(OR}^1\text{)}_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme **16** depicts the conversion of the compounds **15.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **4** in which X is sulfur. In this procedure, the compounds **15.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **4**.

#### **Preparation of the phosphonate ester intermediates **5** in which X is a direct bond**

Schemes **17** and **18** illustrate the preparation of the phosphonate esters **5** in which X is a direct bond. As shown in Scheme **17**, the oxirane **9.2** is reacted, as described in Scheme **1**, with the decahydroisoquinoline derivative **17.1** to produce the hydroxyamine **17.2**. The preparation of the decahydroisoquinoline derivatives **17.1** is described in Schemes **192 - 197**. The product is then transformed, as described previously, (Scheme **3**) into the amide **17.3**.

The reactions shown in Scheme **17** illustrate the preparation of the compounds **17.3** in which the substituent A is either the group  $\text{link-P(O)(OR}^1\text{)}_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme **18** depicts the conversion of the compounds **17.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **5** in which X is a direct bond. In this procedure, the compounds **17.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **5**.

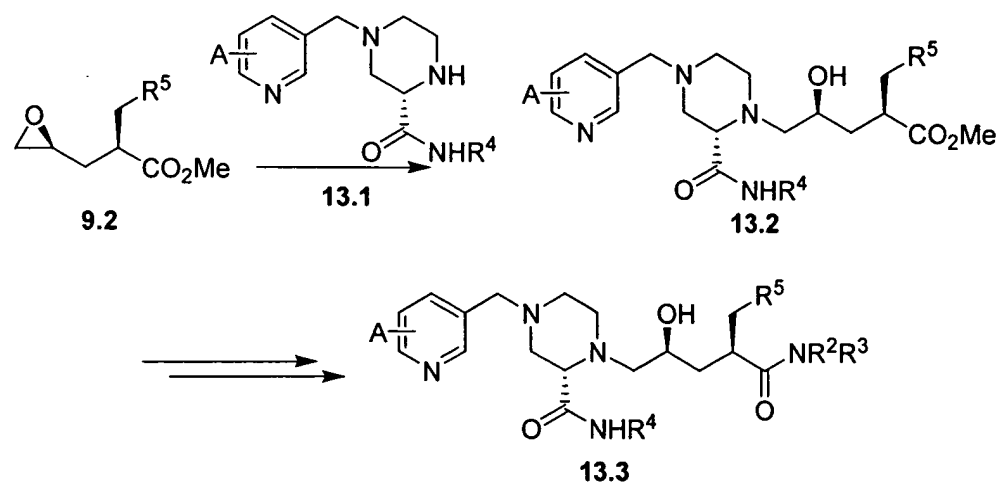
#### **Preparation of the phosphonate ester intermediates **5** in which X is sulfur**

Schemes **19** and **20** illustrate the preparation of the phosphonate esters **5** in which X is sulfur. As shown in Scheme **19**, the benzyl-protected oxirane **3.3** is reacted, as described above,

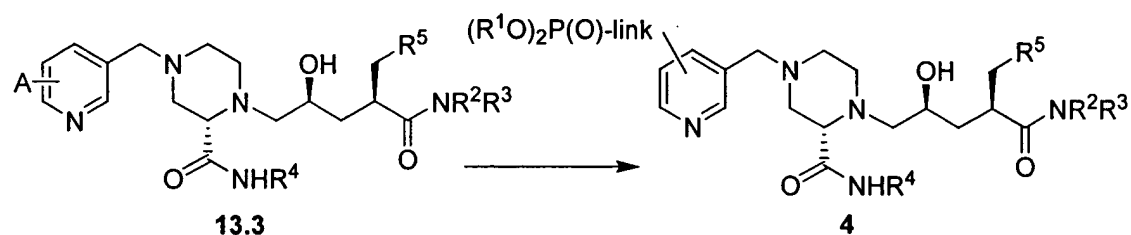
with the decahydroisoquinoline derivative **17.1** to afford the hydroxyamine **19.1**. The product is then converted, as described above (Scheme 5) into the aminoamide **19.2**.

The reactions shown in Scheme 19 illustrate the preparation of the compounds **19.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 20 depicts the conversion of the compounds **19.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **5** in which X is sulfur. In this procedure, the compounds **19.2** are converted, using the procedures described below, Schemes 133 - 197, into the compounds **5**.

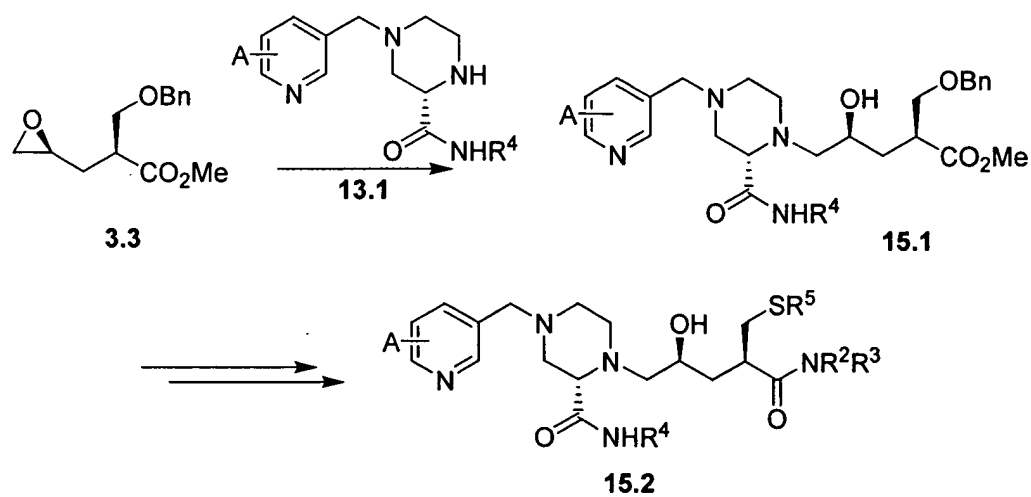
**Scheme 13**



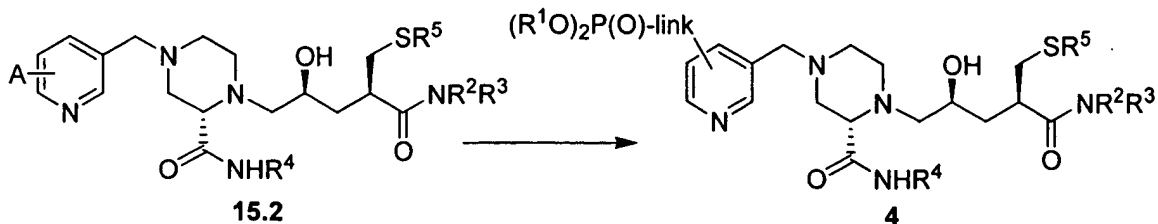
**Scheme 14**



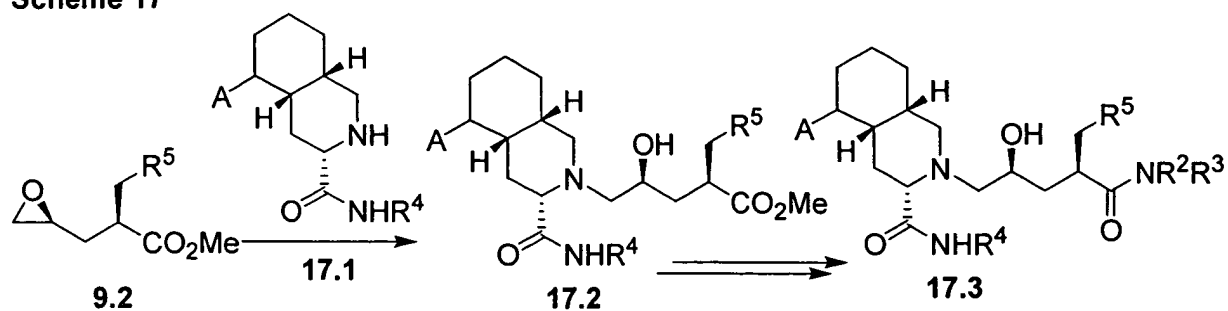
**Scheme 15**



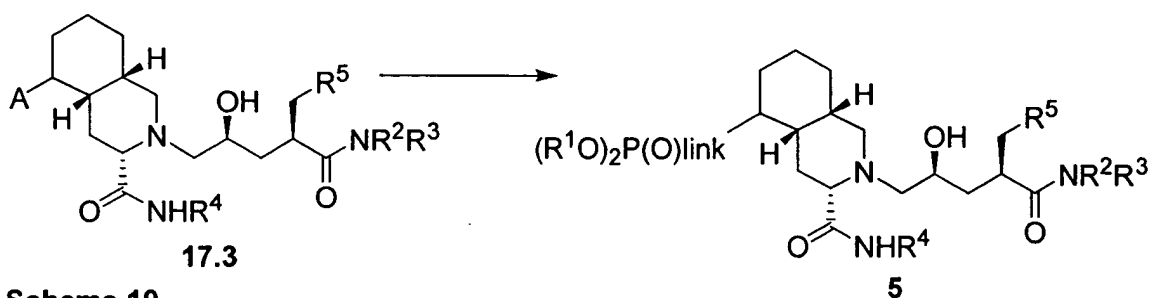
**Scheme 16**



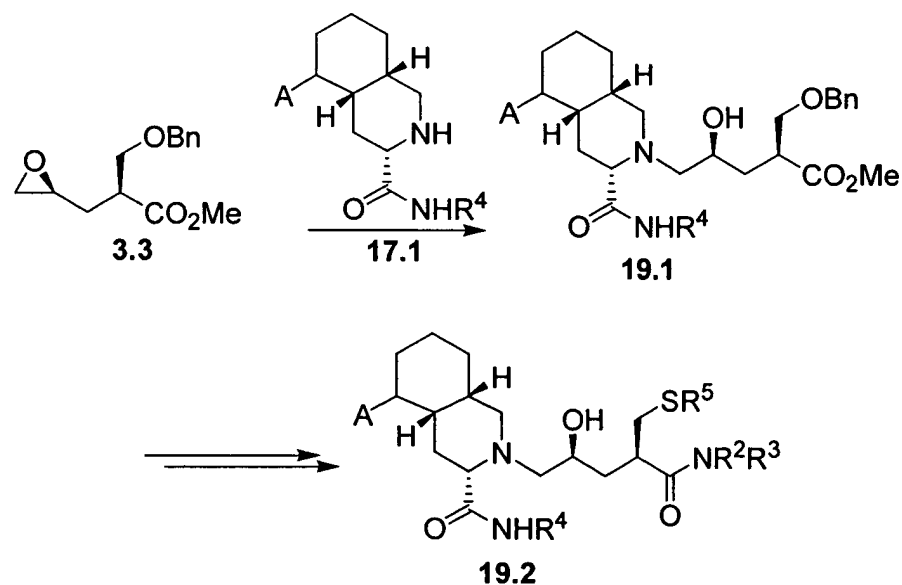
**Scheme 17**



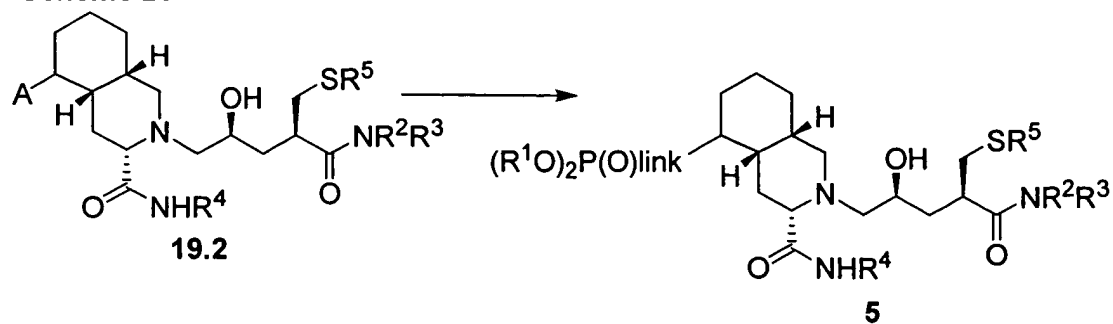
**Scheme 18**



**Scheme 19**



**Scheme 20**



### **Preparation of the phosphonate ester intermediates 6 in which X is a direct bond**

Schemes 21 and 22 illustrate the preparation of the phosphonate esters 6 in which X is a direct bond. As shown in Scheme 21, the glycidyl tosylate 1.4 is reacted, as described in Scheme 5, with the anion of the dimethoxyphenyl propionic ester 21.1 to afford the alkylated product 21.2. The preparation of the dimethoxyphenyl propionic ester derivatives 21.1 is described in Scheme 186. The product is then transformed, as described previously, (Scheme 5) into the amide 21.3.

The reactions shown in Scheme 21 illustrate the preparation of the compounds 21.3 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 22 depicts the conversion of the compounds 21.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 6 in which X is a direct bond. In this procedure, the compounds 21.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 6.

### **Preparation of the phosphonate ester intermediates 6 in which X is sulfur**

Schemes 23 and 24 illustrate the preparation of the phosphonate esters 6 in which X is sulfur. As shown in Scheme 23, the mesylate 3.7 is reacted, as described in Scheme 3, with the dimethoxyphenyl mercaptan 23.1 to yield the thioether 23.2. The preparation of the substituted thiols 23.1 is described below in Schemes 170 – 173. The product is then converted, as described above (Scheme 5) into the aminoamide 23.3.

The reactions shown in Scheme 23 illustrate the preparation of the compounds 23.3 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 24 depicts the conversion of the compounds 23.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 6 in which X is sulfur. In this procedure, the compounds 23.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 6.

### **Preparation of the phosphonate ester intermediates 7 in which X is a direct bond**

Schemes 25 and 26 illustrate the preparation of the phosphonate esters 7 in which X is a direct bond. As shown in Scheme 25, the oxirane 9.2 is reacted, as described above (Scheme 1) with the amine 1.6 to afford the hydroxyamine 25.1. The product is then converted into the silyl ether 25.2, using the procedures described in Scheme 3. The methyl ester is then hydrolyzed to

give the carboxylic acid **25.3**, and this compound is then coupled with the tert. butylamine derivative **25.4**, using the procedures described in Scheme 1, to yield the amide **25.5**. The preparation of the tert. butylamine derivatives **25.4** is described in Schemes 154 – 157.

Desilylation then produces the hydroxyamide **25.6**.

The reactions shown in Scheme 25 illustrate the preparation of the compounds **25.6** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 26 depicts the conversion of the compounds **25.6** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **7** in which X is a direct bond. In this procedure, the compounds **25.6** are converted, using the procedures described below, Schemes 133 - 197, into the compounds **7**.

#### **Preparation of the phosphonate ester intermediates 7 in which X is sulfur**

Schemes 27 and 28 illustrate the preparation of the phosphonate esters **7** in which X is sulfur. As shown in Scheme 27, the carboxylic acid **3.10** is coupled, as described in Scheme 3, with the tert. butylamine derivative **25.4** to yield the amide product **27.1**. The product is then desilylated, as described above, to afford the amide **27.2**.

The reactions shown in Scheme 27 illustrate the preparation of the compounds **27.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 28 depicts the conversion of the compounds **27.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **7** in which X is sulfur. In this procedure, the compounds **27.2** are converted, using the procedures described below, Schemes 133 - 197, into the compounds **7**.

#### **Preparation of the phosphonate ester intermediates 8 in which X is a direct bond**

Schemes 29 and 30 illustrate the preparation of the phosphonate esters **8** in which X is a direct bond. As shown in Scheme 29, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme 1) with the amine **29.1** to afford the amide **29.2** which upon desilylation produces the hydroxyamide **29.3**. The preparation of the ethanolamine derivatives **29.1** is described in Schemes 174 – 178.

The reactions shown in Scheme 29 illustrate the preparation of the compounds **29.3** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 30 depicts the conversion of the compounds **29.3** in which A is [OH], [SH],

[NH], Br, into the phosphonate esters **8** in which X is a direct bond. In this procedure, the compounds **29.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **8**.

#### **Preparation of the phosphonate ester intermediates **8** in which X is sulfur**

Schemes **31** and **32** illustrate the preparation of the phosphonate esters **8** in which X is sulfur. As shown in Scheme **31**, the carboxylic acid **3.10** is coupled, as described previously, with the ethanolamine derivative **29.1** to yield the amide; the product is then desilylated, as described above, to afford the hydroxyamide **31.1**.

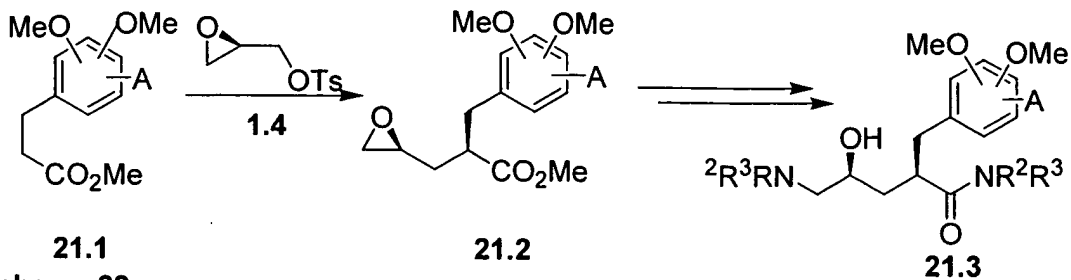
The reactions shown in Scheme **31** illustrate the preparation of the compounds **31.1** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **32** depicts the conversion of the compounds **31.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **8** in which X is sulfur. In this procedure, the compounds **31.1** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **8**.

#### **Preparation of the phosphonate ester intermediates **9** in which X is a direct bond**

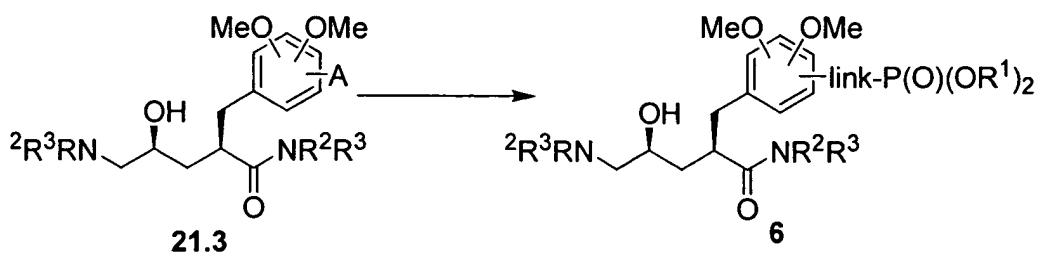
Schemes **33** and **34** illustrate the preparation of the phosphonate esters **9** in which X is a direct bond. As shown in Scheme **33**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the chroman amine **33.1** to afford the corresponding amide, which upon desilylation produces the hydroxyamide **33.2**. The preparation of the chroman amines **33.1** is described in Schemes **179 - 181a**.

The reactions shown in Scheme **33** illustrate the preparation of the compounds **33.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **34** depicts the conversion of the compounds **33.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **9** in which X is a direct bond. In this procedure, the compounds **33.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **9**.

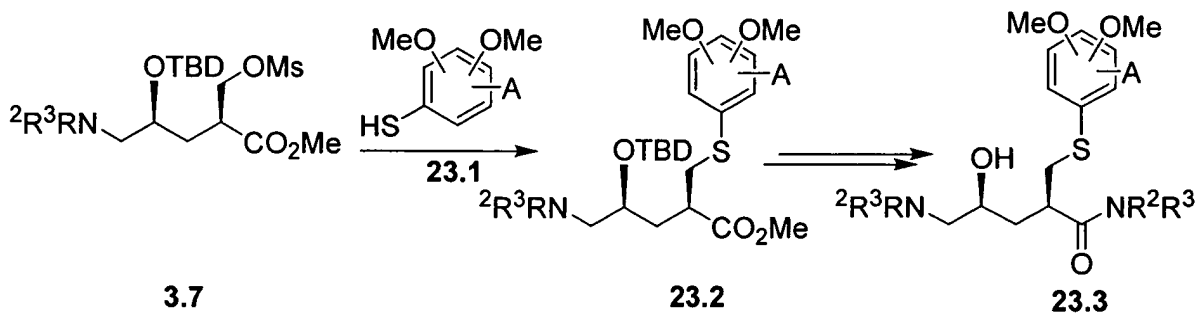
**Scheme 21**



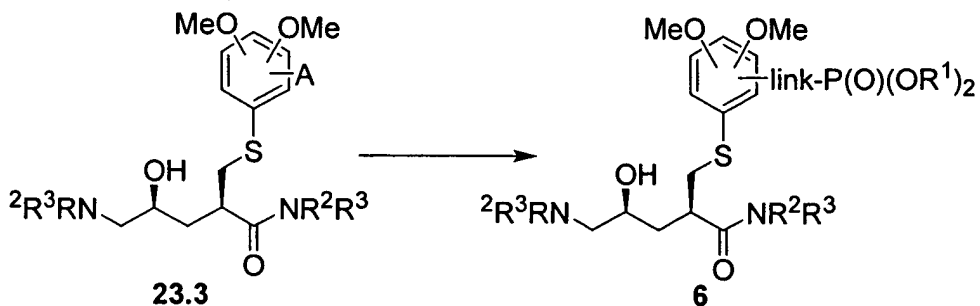
**Scheme 22**



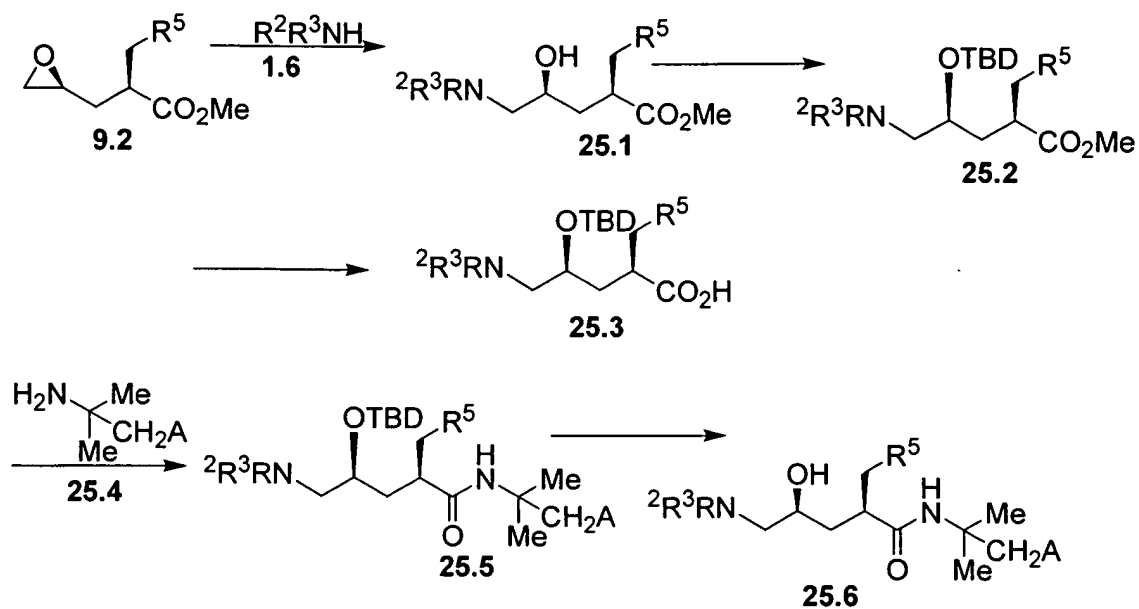
**Scheme 23**



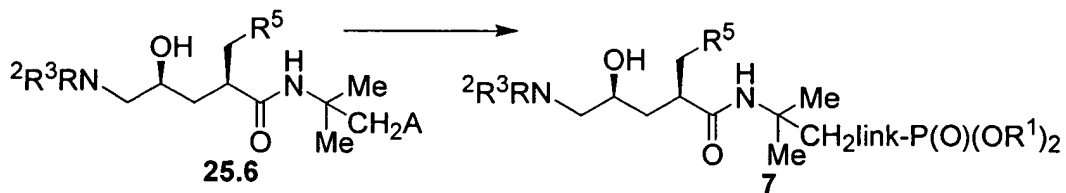
**Scheme 24**



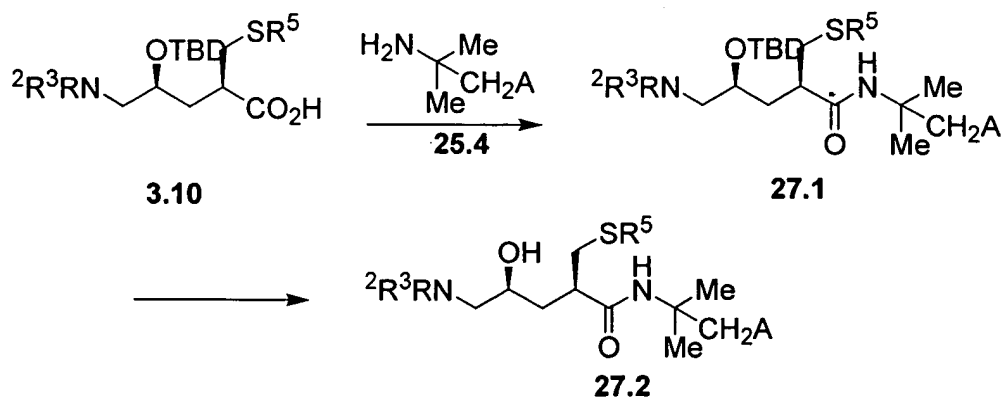
**Schem 25**



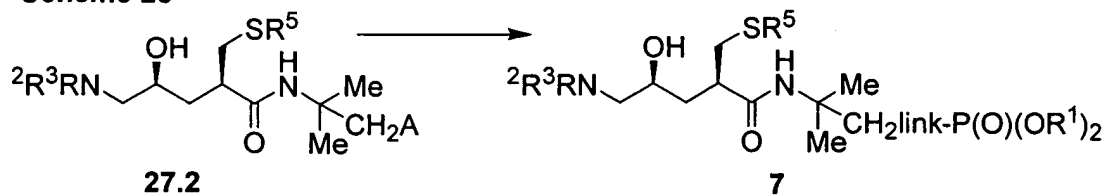
**Scheme 26**



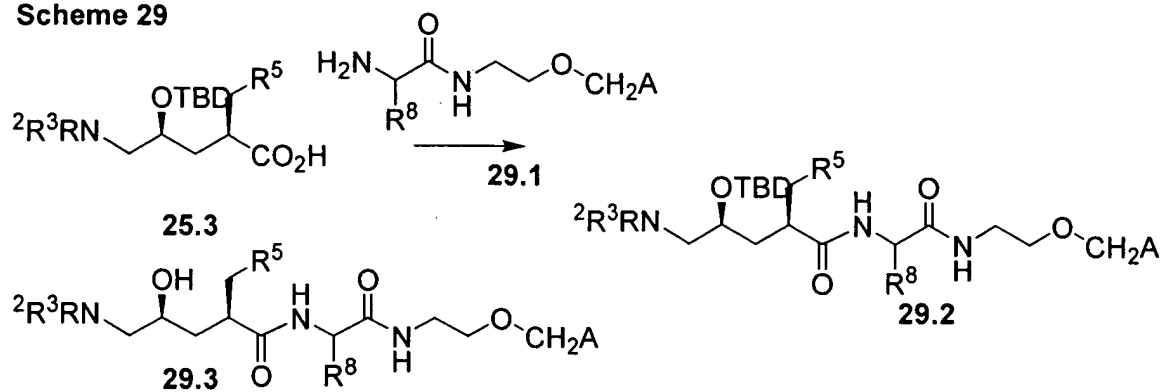
**Scheme 27**



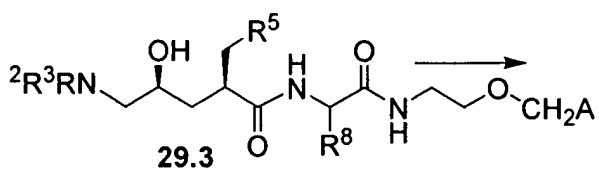
**Scheme 28**



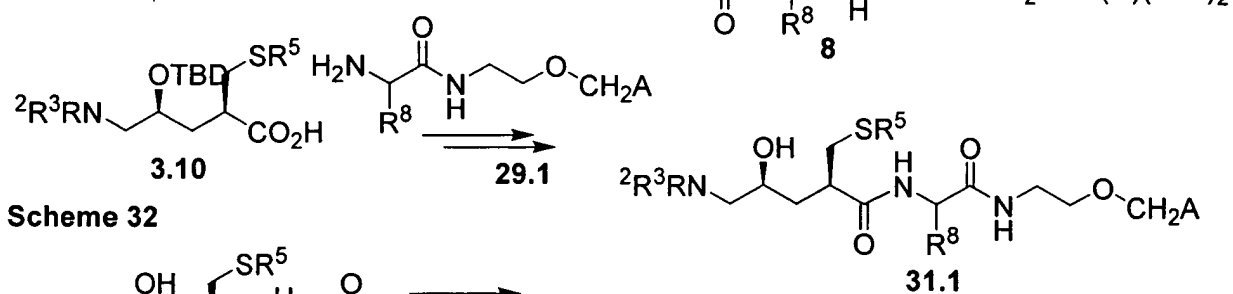
**Scheme 29**



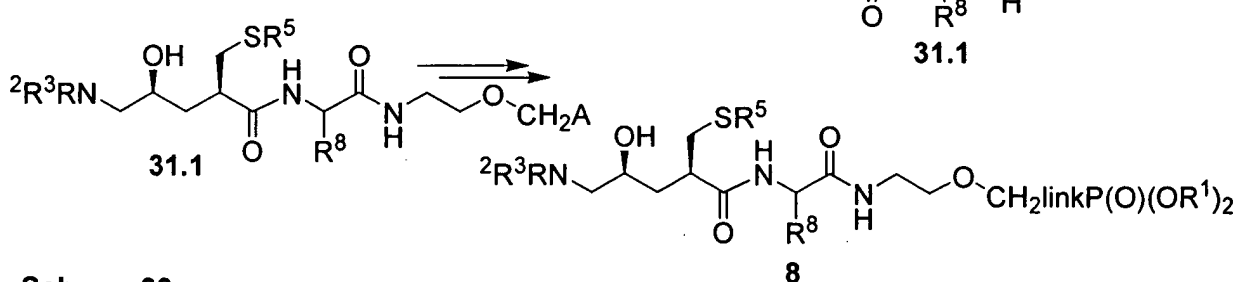
**Scheme 30**



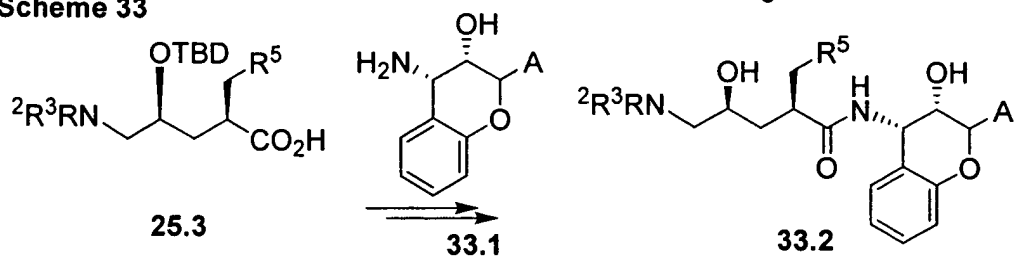
**Scheme 31**



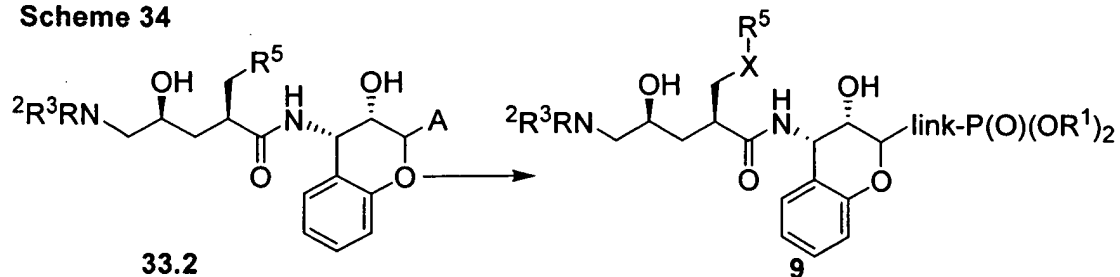
**Scheme 32**



**Scheme 33**



**Scheme 34**



### **Preparation of the phosphonate ester intermediates 9 in which X is sulfur**

Schemes 35 and 36 illustrate the preparation of the phosphonate esters 9 in which X is sulfur. As shown in Scheme 35, the carboxylic acid 3.10 is coupled, as described previously, with the chroman amine 33.1 to yield the amide; the product is then desilylated, as described above, to afford the amide 35.1.

The reactions shown in Scheme 35 illustrate the preparation of the compounds 35.1 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 36 depicts the conversion of the compounds 35.1 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 9 in which X is sulfur. In this procedure, the compounds 35.1 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 9.

### **Preparation of the phosphonate ester intermediates 10 in which X is a direct bond**

Schemes 37 and 38 illustrate the preparation of the phosphonate esters 10 in which X is a direct bond. As shown in Scheme 37, the silylated carboxylic acid 25.3 is coupled, as described above, (Scheme 1) with the phenylalanine derivative 37.1 to afford the corresponding amide, which upon desilylation produces the hydroxyamide 37.2. The preparation of the phenylalanine derivatives 37.1 is described in Schemes 182 – 185.

The reactions shown in Scheme 37 illustrate the preparation of the compounds 37.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 38 depicts the conversion of the compounds 37.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 10 in which X is a direct bond. In this procedure, the compounds 37.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 10.

### **Preparation of the phosphonate ester intermediates 10 in which X is sulfur**

Schemes 39 and 40 illustrate the preparation of the phosphonate esters 10 in which X is sulfur. As shown in Scheme 39, the carboxylic acid 3.10 is coupled, as described previously, with the phenylalanine derivative 37.1 to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide 39.1.

The reactions shown in Scheme 39 illustrate the preparation of the compounds 39.1 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH],

[NH], Br. Scheme 40 depicts the conversion of the compounds 39.1 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 10 in which X is sulfur. In this procedure, the compounds 39.1 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 10.

#### **Preparation of the phosphonate ester intermediates 11 in which X is a direct bond**

Schemes 41 and 42 illustrate the preparation of the phosphonate esters 11 in which X is a direct bond. As shown in Scheme 41, the silylated carboxylic acid 25.3 is coupled, as described above, (Scheme 1) with the decahydroisoquinoline carboxamide 41.1, prepared as described in Scheme 158, to afford the corresponding amide, which upon desilylation produces the hydroxyamide 41.2.

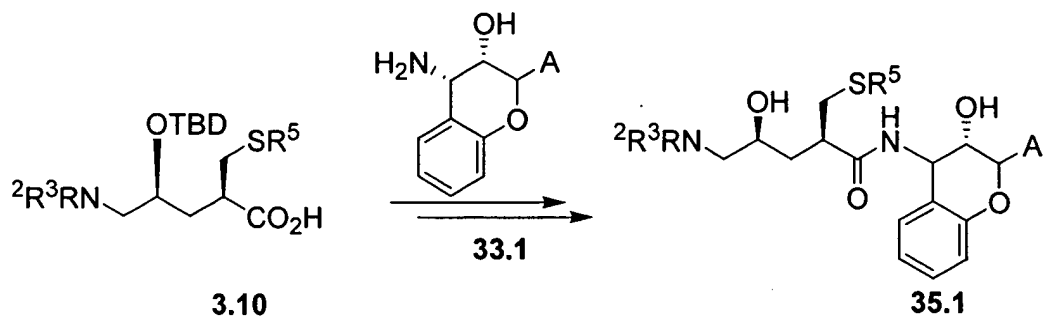
The reactions shown in Scheme 41 illustrate the preparation of the compounds 41.2 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 42 depicts the conversion of the compounds 41.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 11 in which X is a direct bond. In this procedure, the compounds 41.2 are converted, using the procedures described below, Schemes 133 - 197, into the compound

#### **Preparation of the phosphonate ester intermediates 11 in which X is sulfur**

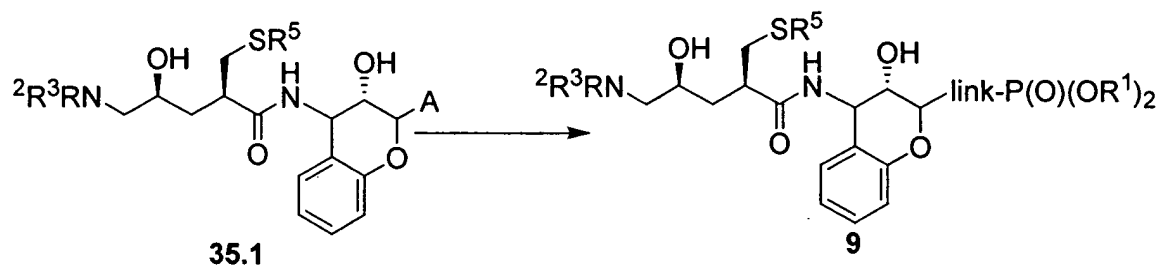
Schemes 43 and 44 illustrate the preparation of the phosphonate esters 11 in which X is sulfur. As shown in Scheme 43, the carboxylic acid 3.10 is coupled, as described previously, with the decahydroisoquinoline carboxamide 41.1 to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide 43.1.

The reactions shown in Scheme 43 illustrate the preparation of the compounds 43.1 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 44 depicts the conversion of the compounds 43.1 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 11 in which X is sulfur. In this procedure, the compounds 43.1 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 11.

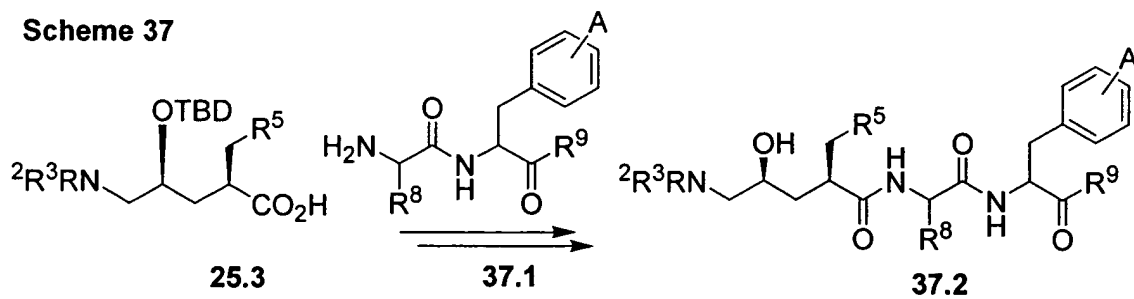
**Scheme 35**



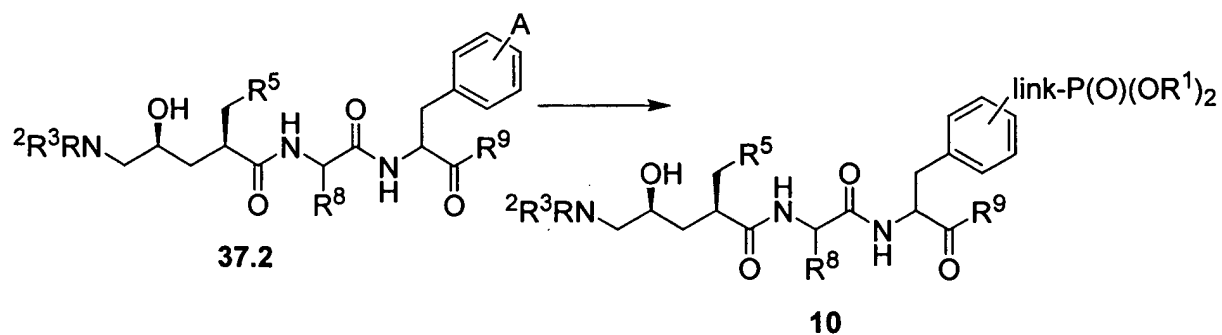
**Scheme 36**



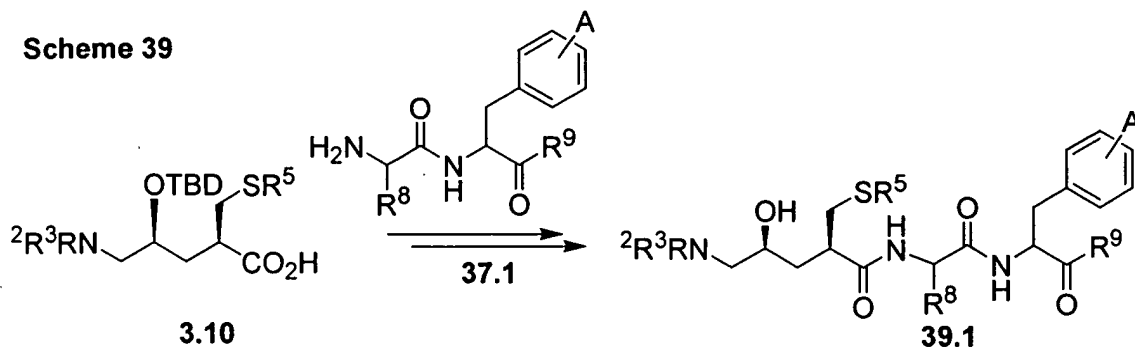
**Scheme 37**



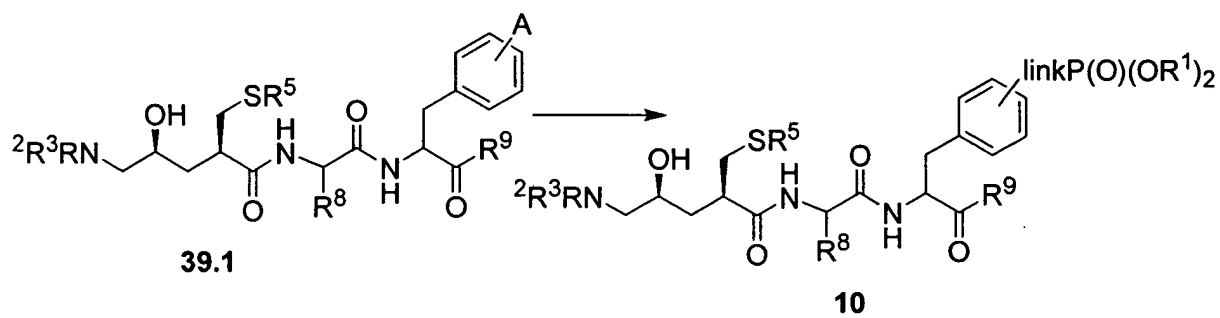
**Scheme 38**



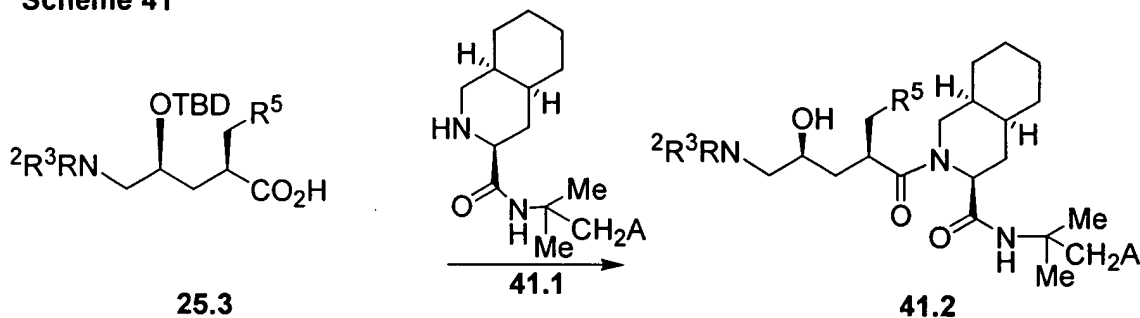
**Scheme 39**



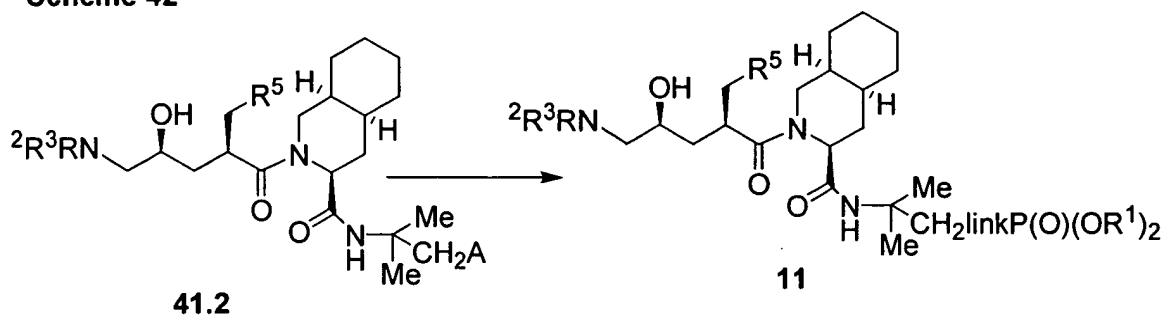
**Scheme 40**



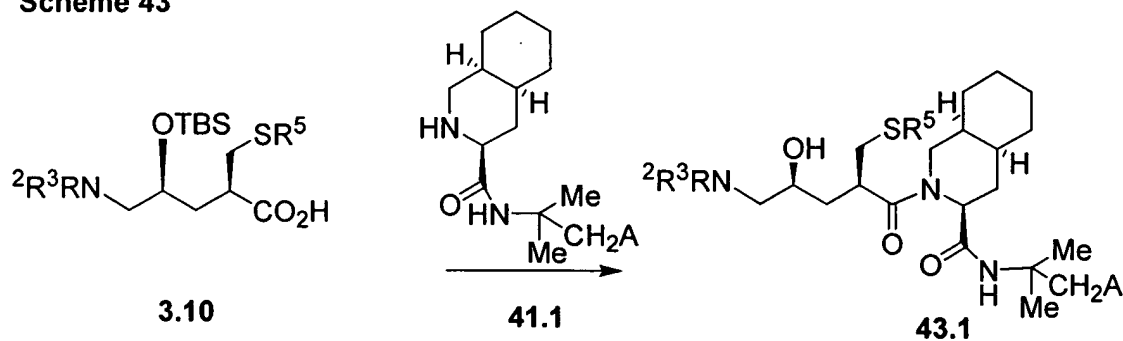
**Scheme 41**



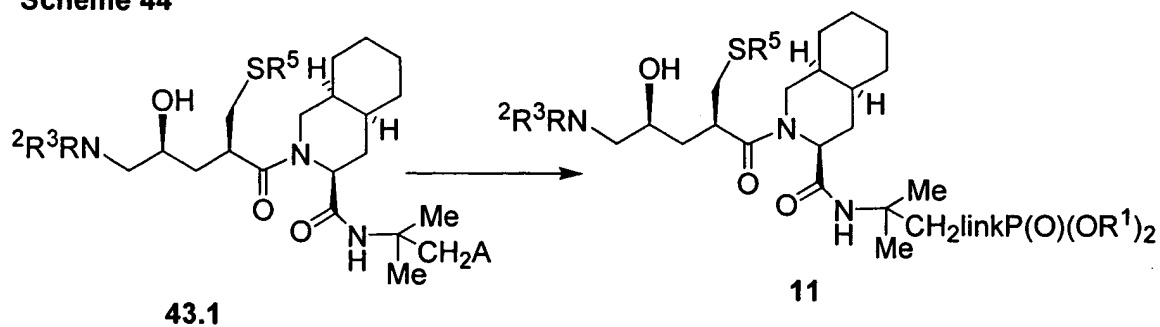
**Scheme 42**



**Scheme 43**



**Scheme 44**



**Preparation of the phosphonate ester intermediates 12 in which X is a direct bond**

Schemes 45 and 46 illustrate the preparation of the phosphonate esters 12 in which X is a direct bond. As shown in Scheme 45, the silylated carboxylic acid 25.3 is coupled, as described above, (Scheme 1) with the decahydroisoquinoline derivative 45.1 to afford the corresponding

amide, which upon desilylation produces the hydroxyamide **45.2**. The preparation of the decahydroisoquinoline derivatives **45.1** is described in Schemes **192 – 197**.

The reactions shown in Scheme **45** illustrate the preparation of the compounds **45.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **46** depicts the conversion of the compounds **45.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **12** in which X is a direct bond. In this procedure, the compounds **45.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **12**.

#### **Preparation of the phosphonate ester intermediates 12 in which X is sulfur**

Schemes **47** and **48** illustrate the preparation of the phosphonate esters **12** in which X is sulfur. As shown in Scheme **47**, the carboxylic acid **3.10** is coupled, as described previously, with the decahydroisoquinoline derivative **45.1** to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide **47.1**.

The reactions shown in Scheme **47** illustrate the preparation of the compounds **47.1** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **48** depicts the conversion of the compounds **47.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **12** in which X is sulfur. In this procedure, the compounds **47.1** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **12**.

#### **Preparation of the phosphonate ester intermediates 13 in which X and X' are direct bonds**

Schemes **49** and **50** illustrate the preparation of the phosphonate esters **12** in which X and X' are direct bonds. As shown in Scheme **49**, a BOC-protected aminoacid **49.1** is converted into the corresponding aldehyde **49.2**. A number of methods are known for the conversion of carboxylic acids and derivatives into the corresponding aldehydes, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 619-627. The conversion is effected by direct reduction of the carboxylic acid, for example employing diisobutyl aluminum hydride, as described in *J. Gen. Chem. USSR.*, 34, 1021, 1964, or alkyl borane reagents, for example as described in *J. Org. Chem.*, 37, 2942, 1972. Alternatively, the carboxylic acid is converted into an amide, such as the N-methoxy N-methyl amide, and the latter compound is reduced with lithium aluminum hydride, for example as described in *J. Med.*

*Chem.*, 1994, 37, 2918, to afford the aldehyde. Alternatively, the carboxylic acid is reduced to the corresponding carbinol which is then oxidized to the aldehyde. The reduction of carboxylic acids to carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 548ff. The reduction reaction is performed by the use of reducing agents such as borane, as described in *J. Am. Chem. Soc.*, 92, 1637, 1970, or by lithium aluminum hydride, as described in *Org. React.*, 6, 649, 1951. The resultant carbinol is then converted into the aldehyde by means of an oxidation reaction. The oxidation of a carbinol to the corresponding aldehyde is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The conversion is effected by the use of oxidizing agents such as pyridinium chlorochromate, as described in *J. Org. Chem.*, 50, 262, 1985, or silver carbonate, as described in *Compt. Rend. Ser. C.*, 267, 900, 1968, or dimethyl sulfoxide/acetic anhydride, as described in *J. Am. Chem. Soc.*, 87, 4214, 1965. Preferably, the procedure described in EP 708085 is employed. The carboxylic acid **49.1** is first reacted with equimolar amounts of isobutyl chloroformate and triethylamine in tetrahydrofuran, to afford a mixed anhydride which is then reduced by treatment with sodium borohydride in aqueous tetrahydrofuran at ambient temperature to afford the carbinol **49.2**. The carbinol is then oxidized to the aldehyde **49.3** by reaction with oxalyl chloride and dimethylsulfoxide in dichloromethane at -60°C, as described in EP708085. To transform the aldehyde into the hydroxyester **49.5**, ethyl 3-iodopropionate **49.4** is reacted first with a zinc-copper couple, prepared as described in *Org. Syn. Coll.* Vol. 5, 855, 1973, and the product is then reacted with trichlorotitanium isopropoxide, as described in EP 708085. The resultant reagent is then treated with the aldehyde **49.3** in dichloromethane at -20°C to yield the hydroxyester **49.5**. The hydroxyester is then cyclized to the lactone **49.6** by treatment with acetic acid in toluene at 100°C, as described in EP 708085. A number of alternative preparations of the lactone **49.6** are known, for example as described in *J. Org. Chem.*, 1985, 50, 4615, *J. Org. Chem.*, 1995, 60, 7927 and *J. Org. Chem.*, 1991, 56, 6500. The lactone **49.6** is then reacted with a substituted benzyl iodide **49.7** to afford the alkylated product **49.8**. The preparation of the benzyl halides **49.7** is described below, (Schemes 165 – 169). The alkylation reaction is performed in an aprotic organic solvent such as dimethylformamide or tetrahydrofuran, in the presence of a strong base such as sodium hydride or lithium hexamethyl disilylazide. Preferably, the lactone is first reacted with lithium bis(trimethylsilyl)amide in a mixture of tetrahydrofuran and 1,3-

dimethyltetrahydropyrimidinone, and then ethyl 3-iodopropionate is added, as described in EP 708085, to prepare the alkylated lactone **49.8**. The lactone is then converted into the corresponding hydroxyacid **49.9** by alkaline hydrolysis, for example by treatment with lithium hydroxide in aqueous dimethoxyethane, as described in EP 708085. The hydroxyacid is then converted into the tert. butyldimethylsilyl ether **49.10**, by reaction with excess chloro tert. butyldimethylsilane and imidazole in dimethylformamide, followed by alkaline hydrolysis, employing potassium carbonate in aqueous methanolic tetrahydrofuran, as described in EP 708085, to yield the silyl ether **49.10**. The carboxylic acid is then coupled, as described above (Scheme 5) with the amine  $R^2R^3NH$  to afford the amide product **49.11**. The BOC protecting group is then removed to give the free amine **49.12**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC protecting group is removed by treatment of the substrate with 3M hydrogen chloride in ethyl acetate, as described in *J. Org. Chem.*, 43, 2285, 1978, a procedure which also removes the silyl protecting group to afford the hydroxy amine **49.12**. The latter compound is then coupled with the carboxylic acid  $R^{10}COOH$ , or a functional equivalent thereof, to give the amide or carbamate product **49.13**. The preparation of amides by the reaction between amines and amides is described above (Scheme 1). Compounds in which the group  $R^{10}$  is alkoxy are carbamates; the preparation of carbamates is described below (Scheme 198)

The reactions shown in Scheme 49 illustrate the preparation of the compounds **49.13** in which the substituent A is either the group  $link-P(O)(OR^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 50 depicts the conversion of the compounds **49.13** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X and X' are direct bonds. In this procedure, the compounds **49.13** are converted, using the procedures described below, Schemes 133 - 197, into the compounds **13**.

**Preparation of the phosphonate ester intermediates 13 in which X is a direct bond and X' is sulfur**

Schemes 51 and 52 illustrate the preparation of the phosphonate esters **13** in which X is a direct bond and X' is sulfur. In this procedure, BOC serine methyl ester mesylate, **51.1**, the

preparation of which is described in *Synlett.*, 1997, 169, is reacted with the thiol **51.2**, employing the conditions described in Scheme 3, to prepare the thioether **51.3**. The methyl ester group is then transformed into the corresponding aldehyde **51.4**. The reduction of esters to aldehydes is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 621. The conversion is effected by treatment with diisobutyl aluminum hydride, sodium aluminum hydride, lithium tri-tertiary butoxy aluminum hydride and the like. Preferably, the ester **51.3** is reduced to the aldehyde **51.4** by reaction with the stoichiometric amount of diisobutyl aluminum hydride in toluene at  $-80^{\circ}\text{C}$ , as described in *Synthesis*, 617, 1975. The aldehyde is then transformed into the diamide **51.5**, using the sequence of reactions and reaction conditions described above (Scheme 49) for the conversion of the aldehyde **49.3** into the diamide **49.13**.

The reactions shown in Scheme 51 illustrate the preparation of the compounds **51.5** in which the substituent A is either the group  $\text{link-P(O)(OR}^1\text{)}_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 52 depicts the conversion of the compounds **51.5** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **51.5** are converted, using the procedures described below, Schemes 133 - 197, into the compounds **13**.

#### **Preparation of the phosphonate ester intermediates **13** in which X and X' are sulfur**

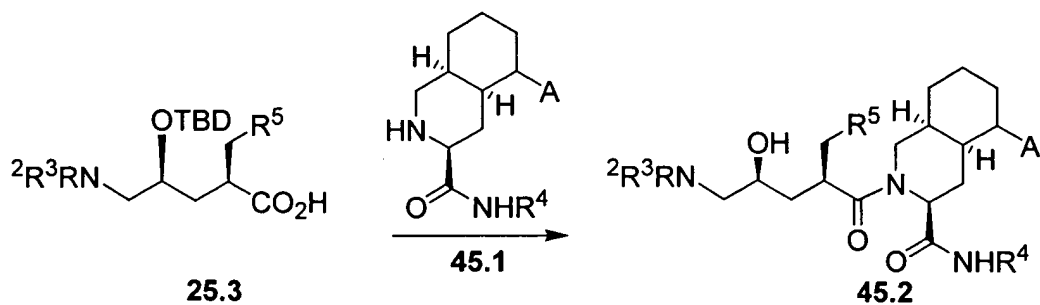
Schemes 53, 54 and 55 illustrate the preparation of the phosphonate esters **13** in which X and X' are sulfur. As shown in Scheme 53, the aldehyde **51.4** is reacted with the dianion of N-methylmethacrylamide **53.1** to form the hydroxyamide **53.2**. The dianion is generated by treatment of N-methylmethacrylamide with two equivalents of an alkylolithium, for example n-butyllithium, in an organic solvent such as tetrahydrofuran or dimethoxyethane, as described in *J. Org. Chem.*, 1986, 51, 3921. The dianion is then reacted with the aldehyde in the presence of chlorotitanium triisopropoxide, to afford the olefinic amide **53.2**. The product is cyclized to produce the methylene lactone **53.3** by heating in an inert solvent such as xylene, at reflux temperature, as described in *J. Org. Chem.*, 1986, 51, 3921. The methylene lactone is then reacted with the thiol **53.4** to yield the thioether **53.5**. The preparation of the thiols **53.4** is described below, (Schemes 170 – 173). The addition of thiols to methylene lactones analogous to the compound **53.3** is described in *J. Org. Chem.*, 1986, 51, 3921. Equimolar amounts of the reactants are combined in an alcoholic solvent such as methanol at about  $60^{\circ}\text{C}$ , in the presence of

a tertiary base such as triethylamine, to give the addition product **53.5**. The latter compound is then subjected to basic hydrolysis, for example by reaction with lithium hydroxide, as described above, (Scheme 49) to produce the hydroxyacid **53.6**. The product is silylated, as described in Scheme 49, to give the silylated carbinol **53.7**, and the product is then converted, as described in Scheme 49, into the diamide **53.8**.

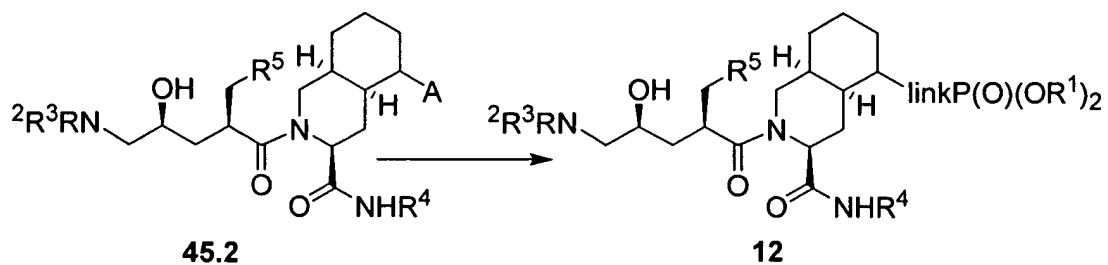
Scheme 54 illustrates an alternative method for the preparation of the diamides **53.8**. In this procedure, the anion of the lactone **54.1**, obtained as an intermediate in the conversion of the aldehyde **51.4** into the diamide **51.5**, (Scheme 51) is reacted with formaldehyde or a functional equivalent thereof, to afford the hydroxymethyl compound **54.2**. The generation of the anion of lactones analogous to **54.1**, and alkylation thereof, is described above in Scheme 49. Preferably, the anion is prepared by reaction of the lactone, in a solvent mixture composed of tetrahydrofuran and 1,3-dimethyltetrahydropyrimidinone, with lithium bis(trimethylsilyl)amide, as described in EP 708085, and formaldehyde, generated by pyrolysis of paraformaldehyde, is then introduced in an inert gas stream. The hydroxymethyl product is then converted into the corresponding mesylate **54.3**, by reaction with methanesulfonyl chloride in dichloromethane containing a tertiary base such as triethylamine or dimethylaminopyridine, and the mesylate is then reacted with the thiol reagent **53.4**, using the procedure described above for the preparation of the thioether **51.3**, to yield the thioether **53.5**. The product is then transformed, as described above, into the diamide **53.8**.

The reactions shown in Schemes 53 and 54 illustrate the preparation of the compounds **53.8** in which the substituent A is either the group  $\text{link-P(O)(OR}^1\text{)}_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 55 depicts the conversion of the compounds **53.8** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X and X' are sulfur. In this procedure, the compounds **53.8** are converted, using the procedures described below, Schemes 133 - 197, into the compounds **13**.

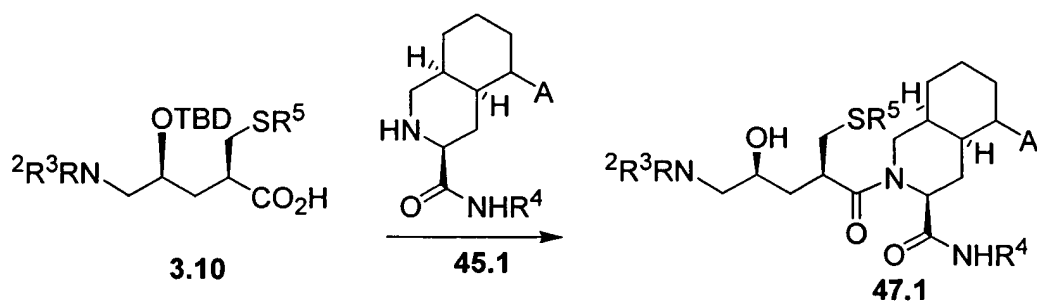
**Scheme 45**



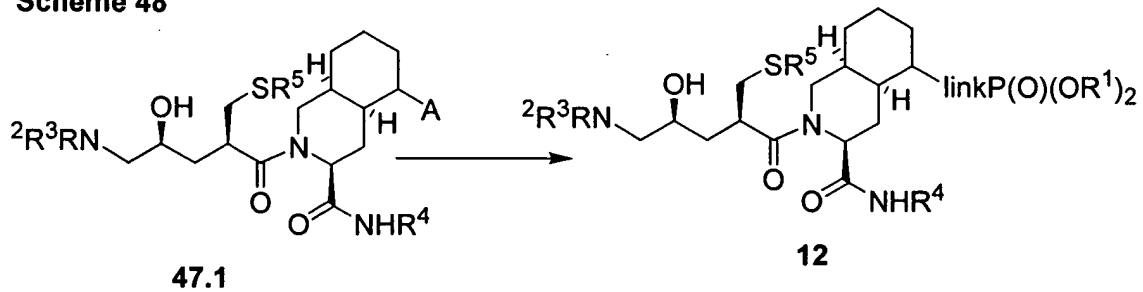
**Scheme 46**



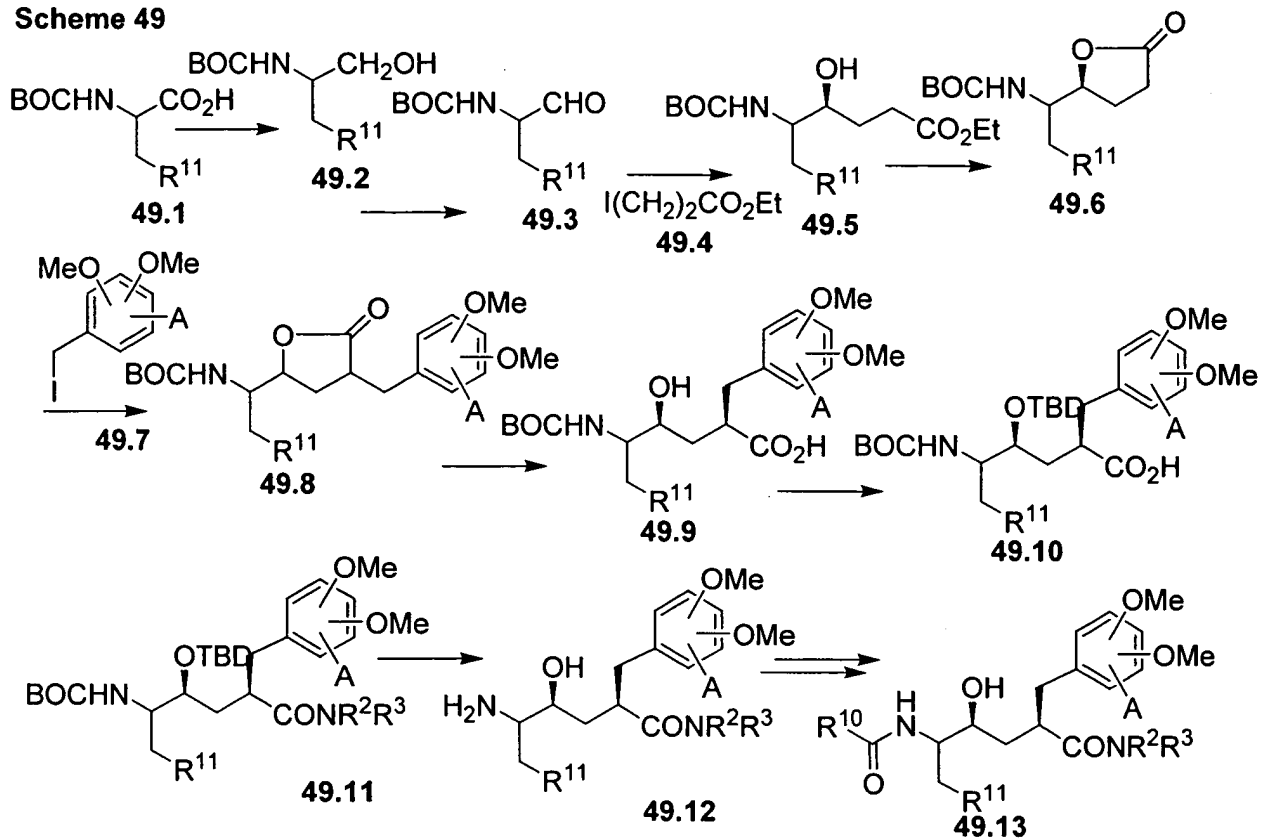
**Scheme 47**



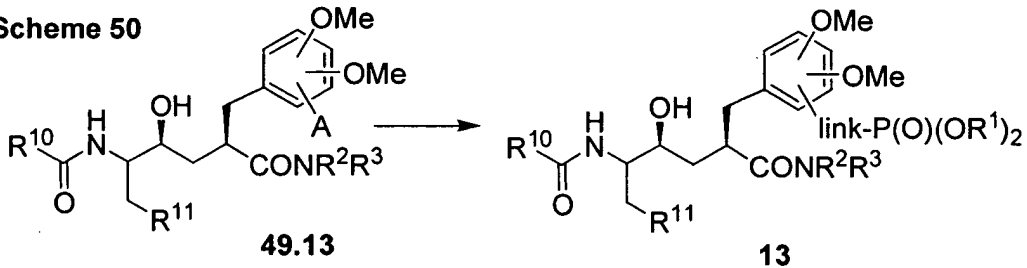
**Scheme 48**



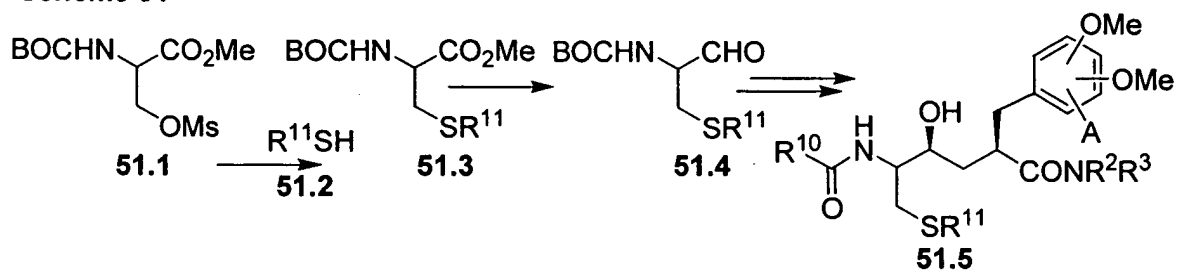
**Scheme 49**



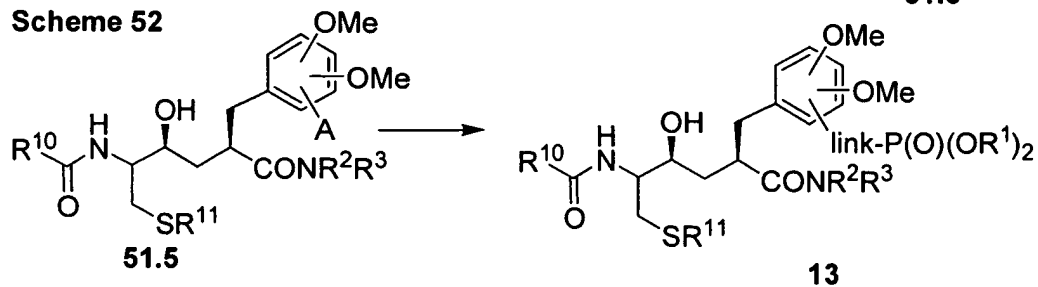
**Scheme 50**



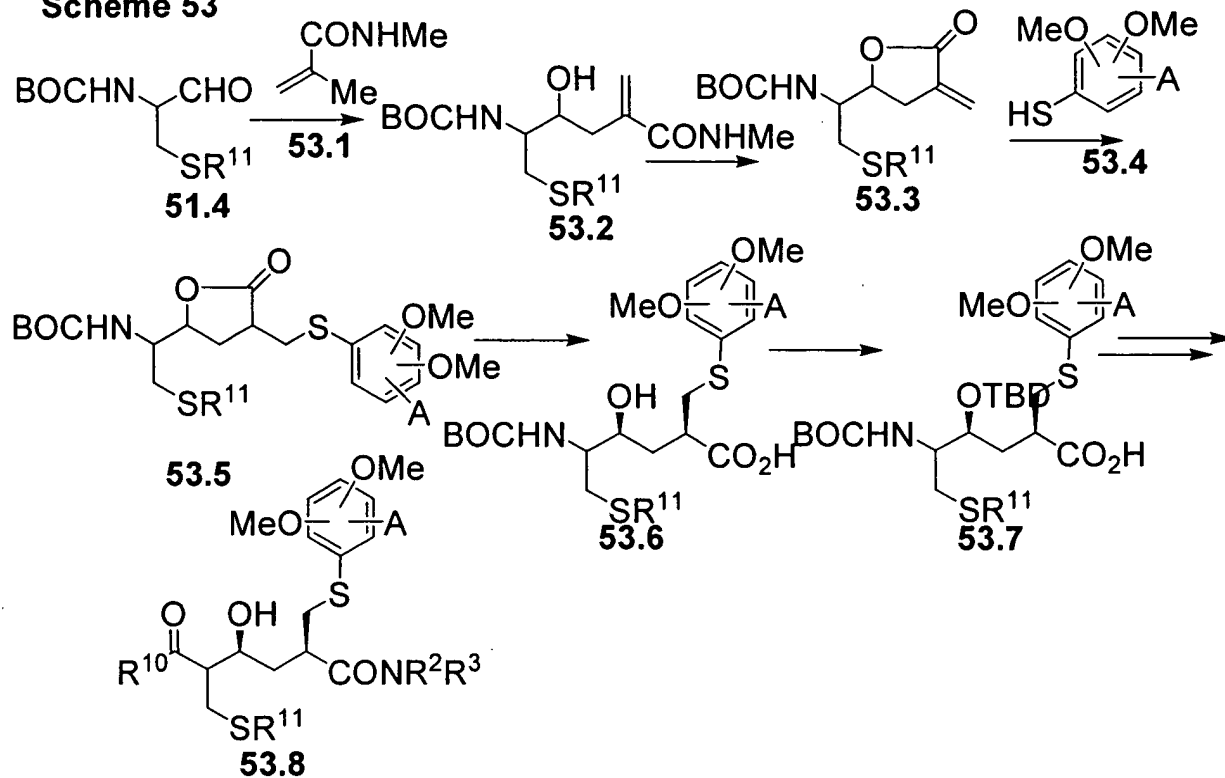
**Scheme 51**



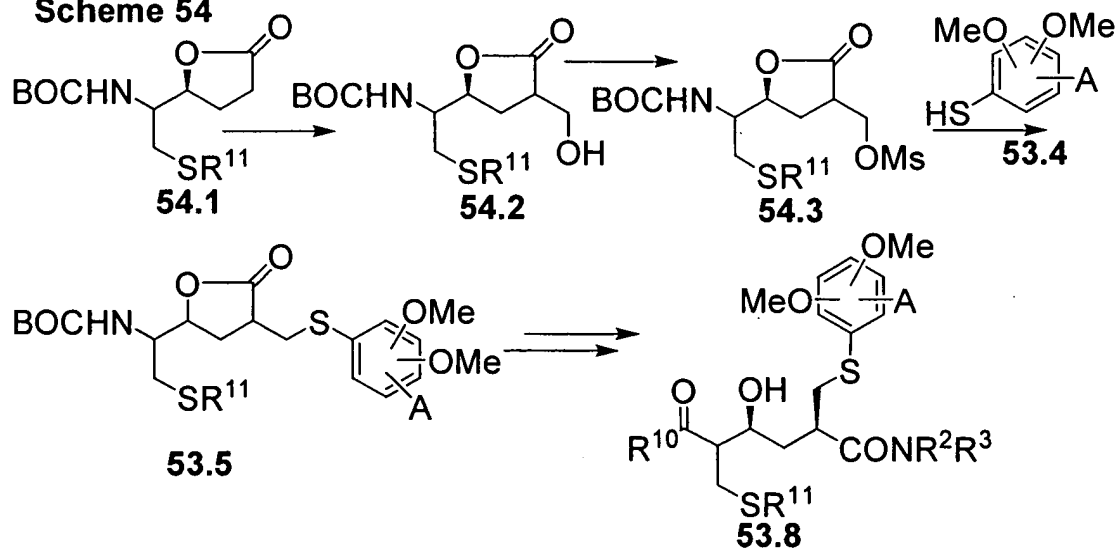
**Scheme 52**



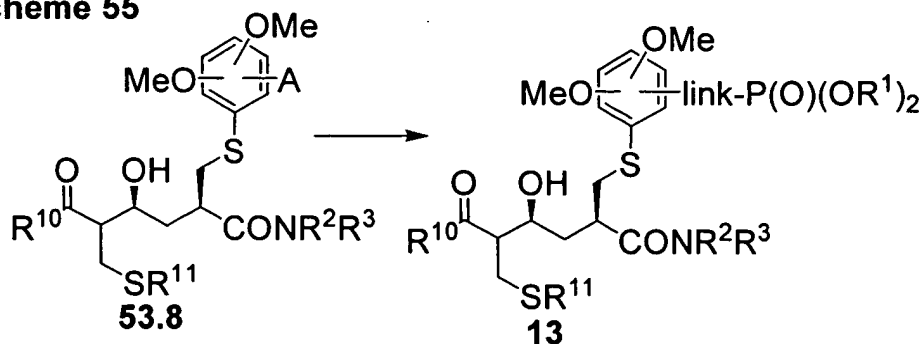
### Scheme 53



### Scheme 54



### Scheme 55



**Preparation of the phosphonate ester intermediates 13 in which X is sulfur and X' is a direct bond**

Schemes 56 and 57 illustrate the preparation of the phosphonate esters 13 in which X is sulfur and X' is a direct bond. In this procedure, the BOC-protected aldehyde 49.3 is converted, as described in Scheme 53, into the methylene lactone 56.1. The lactone is then reacted with the thiol 53.4 and a base, as described in Scheme 53, to yield the thioether 56.2. The thioether is then transformed, as described in Scheme 53, into the diamide 56.3.

The reactions shown in Scheme 56 illustrate the preparation of the compounds 56.3 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 57 depicts the conversion of the compounds 56.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 13 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 56.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 13.

**Preparation of the phosphonate ester intermediates 14 in which X and X' are direct bonds**

Schemes 58 and 59 illustrate the preparation of the phosphonate esters 14 in which X and X' are direct bonds. In this procedure, the lactone 49.6 is reacted, as described in Scheme 49, with a substituted benzyl iodide 58.1, to produce the alkylated compound 58.2. The preparation of the benzyl iodides 58.1 is described in Schemes 187 - 191. The product is then transformed, as described in Scheme 49, into the diamide 58.3.

The reactions shown in Scheme 58 illustrate the preparation of the compounds 58.3 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 59 depicts the conversion of the compounds 58.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 14 in which X and X' are direct bonds. In this procedure, the compounds 58.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 14.

**Preparation of the phosphonate ester intermediates 14 in which X is a direct bond and X' is sulfur**

Schemes 60 and 61 illustrate the preparation of the phosphonate esters 14 in which X is a direct bond and X' is sulfur. In this procedure, the lactone 54.1 is reacted, as described in Scheme 49, with a substituted benzyl iodide 58.1, to produce the alkylated compound 60.1. The product is then transformed, as described in Scheme 49, into the diamide 60.2.

The reactions shown in Scheme 60 illustrate the preparation of the compounds 60.2 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 61 depicts the conversion of the compounds 60.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 14 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 60.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 14.

#### **Preparation of the phosphonate ester intermediates 14 in which X and X' are sulfur**

Schemes 62, 63 and 64 illustrate the preparation of the phosphonate esters 14 in which X and X' are sulfur. As shown in Scheme 62, the methylene lactone 53.3 is reacted, as described in Scheme 53, with a substituted thiophenol 62.1 to produce the addition product 62.2. The preparation of the substituted thiophenols 62.1 is described below, (Schemes 144 – 153). The product is then transformed, as described in Scheme 53, into the diamide 62.3.

Scheme 63 illustrates an alternative method for the preparation of the diamide 62.3. In this procedure, the mesylate 54.3 is reacted, as described in Scheme 54, with the thiol 62.1 to afford the alkylation product 63.1. The product is then transformed, as described in Scheme 53, into the diamide 62.3.

The reactions shown in Schemes 62 and 63 illustrate the preparation of the compounds 62.3 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 64 depicts the conversion of the compounds 62.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 14 in which X and X' are sulfur. In this procedure, the compounds 62.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 14.

#### **Preparation of the phosphonate ester intermediates 14 in which X is sulfur and X' is a direct bond**

Schemes 65 and 66 illustrate the preparation of the phosphonate esters 14 in which X is sulfur and X' is a direct bond. In this procedure, the methylene lactone 56.1 is reacted, as described in Scheme 53, with a substituted thiophenol 62.1, to produce the thioether 65.1. The product is then transformed, as described in Scheme 53, into the diamide 65.2.

The reactions shown in Scheme 65 illustrate the preparation of the compounds 65.2 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH],

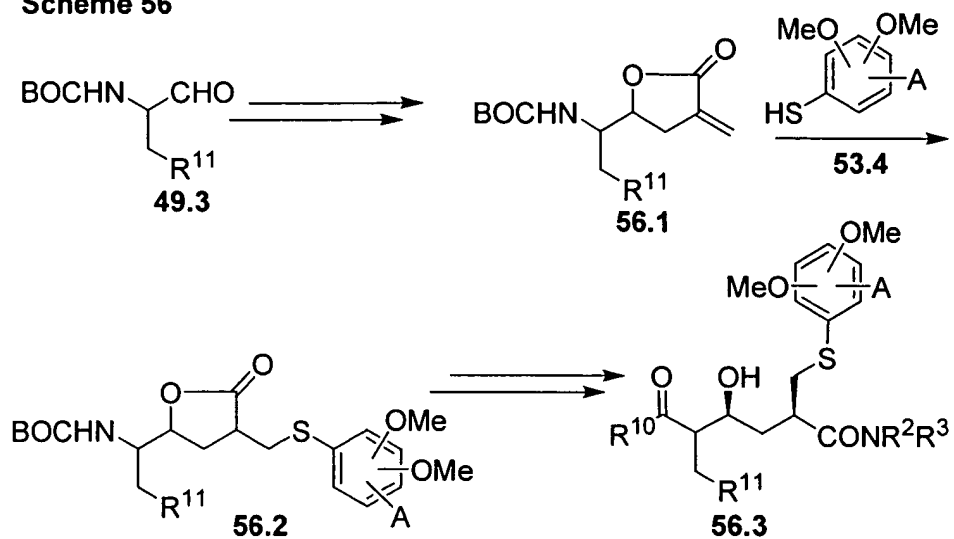
[NH], Br. Scheme 66 depicts the conversion of the compounds 65.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 14 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 65.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 14.

**Preparation of the phosphonate ester intermediates 15 in which X and X' are direct bonds**

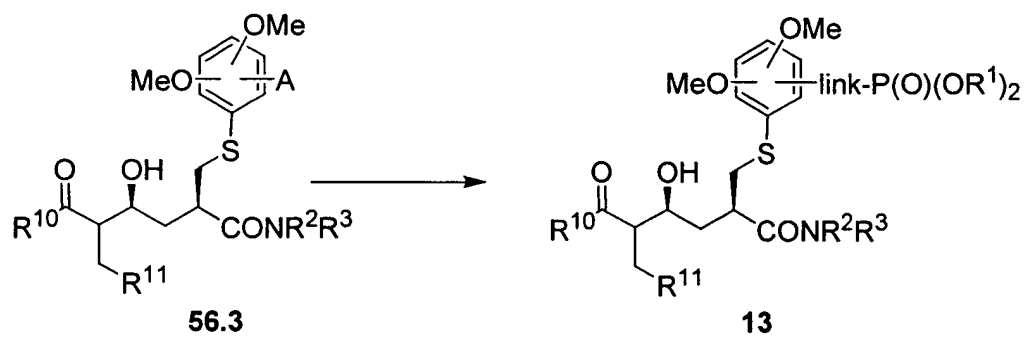
Schemes 67 and 68 illustrate the preparation of the phosphonate esters 15 in which X and X' are direct bonds. In this procedure, the BOC-protected phenylalanine derivative 67.1 is converted into the corresponding aldehyde 67.2, using the procedures described above (Scheme 49). The preparation of the phenylalanine derivatives 67.1 is described below, (Schemes 182 – 184 ). The aldehyde is then converted, using the procedures described in Scheme 49, into the lactone 67.3. The latter compound is then alkylated, as described in Scheme 49, with the reagent  $R^5CH_2I$ , (67.4), to afford the alkylated product 67.5. This compound is then converted, as described in Scheme 49, into the diamide 67.6.

The reactions shown in Scheme 67 illustrate the preparation of the compounds 67.6 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 68 depicts the conversion of the compounds 67.6 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 15 in which X and X' are direct bonds. In this procedure, the compounds 67.6 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 15.

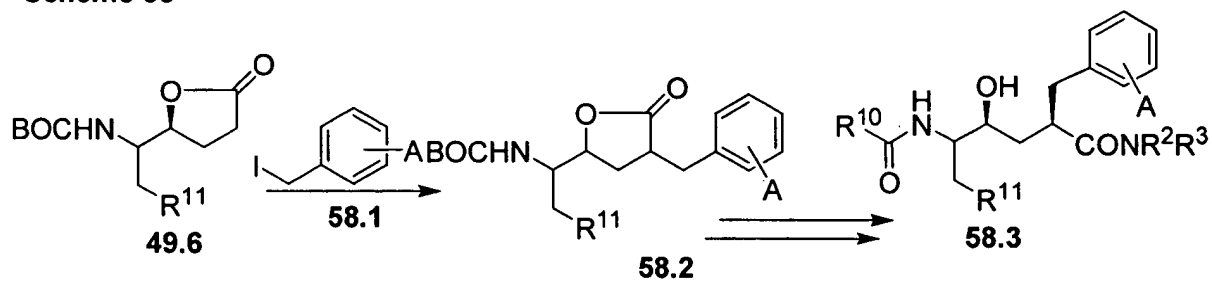
**Scheme 56**



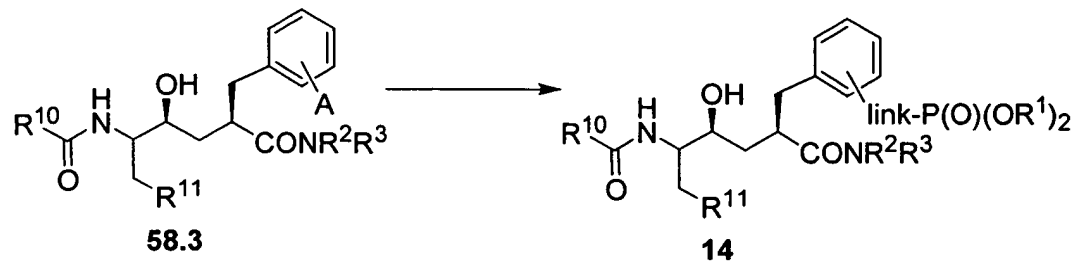
**Scheme 57**



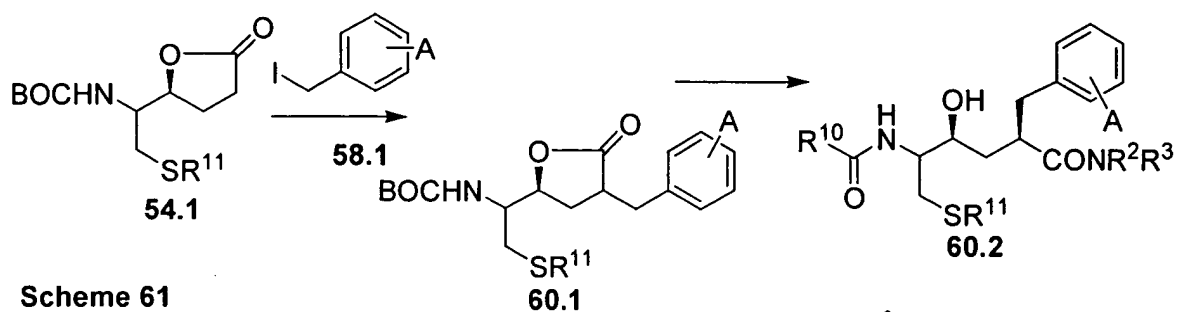
**Scheme 58**



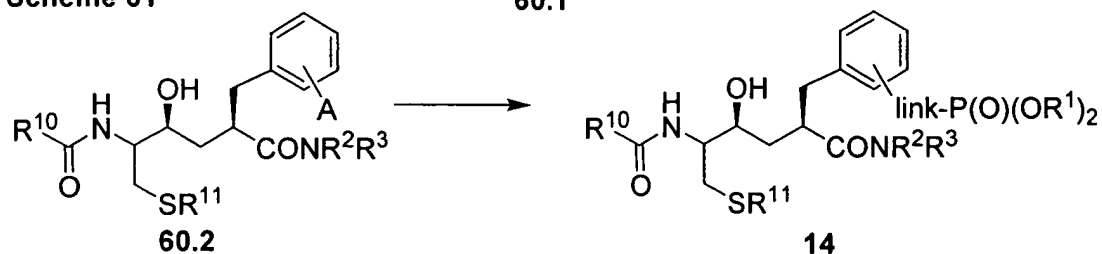
**Scheme 59**



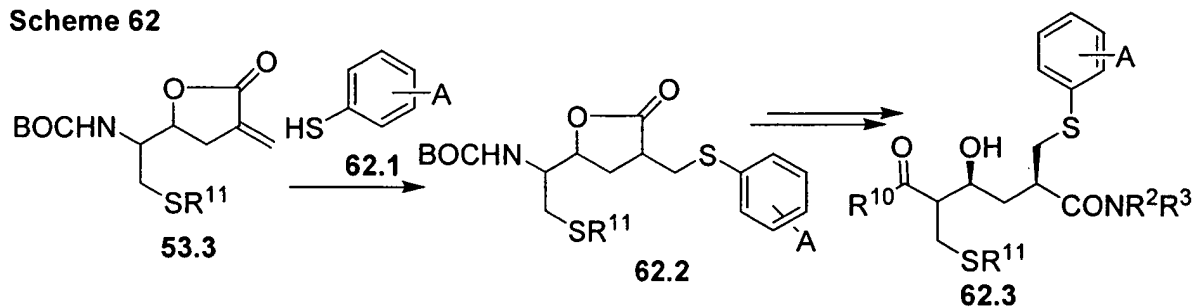
**Scheme 60**



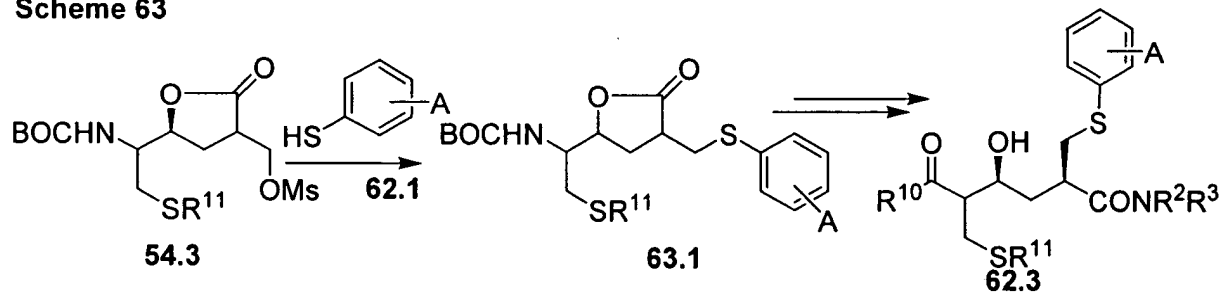
**Scheme 61**



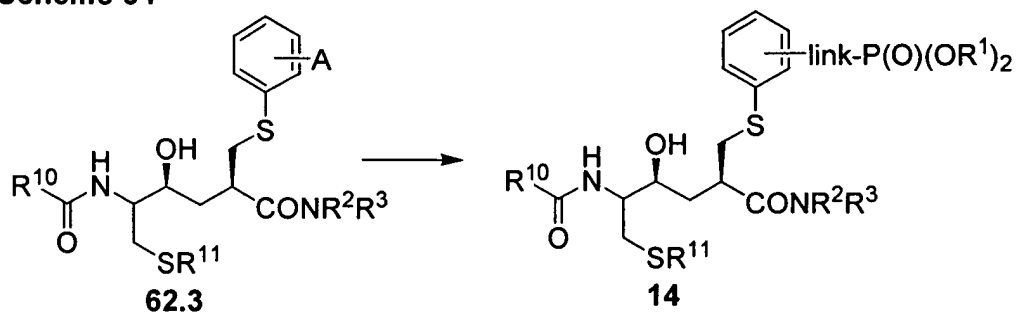
**Scheme 62**



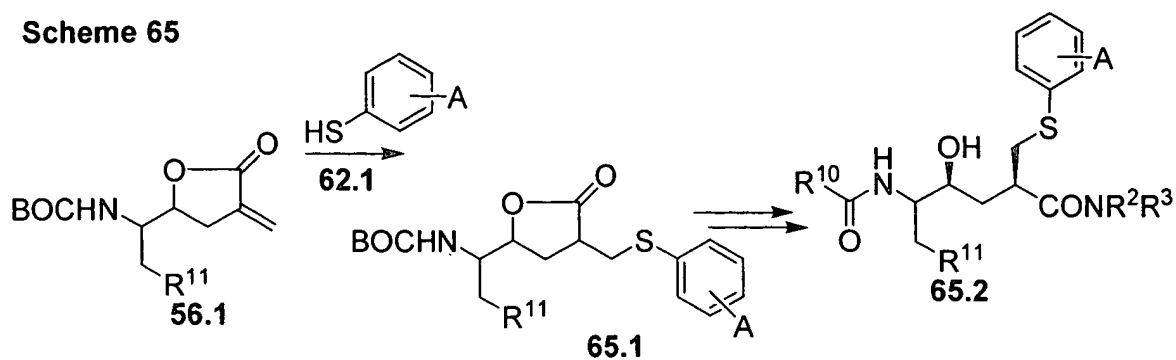
**Scheme 63**



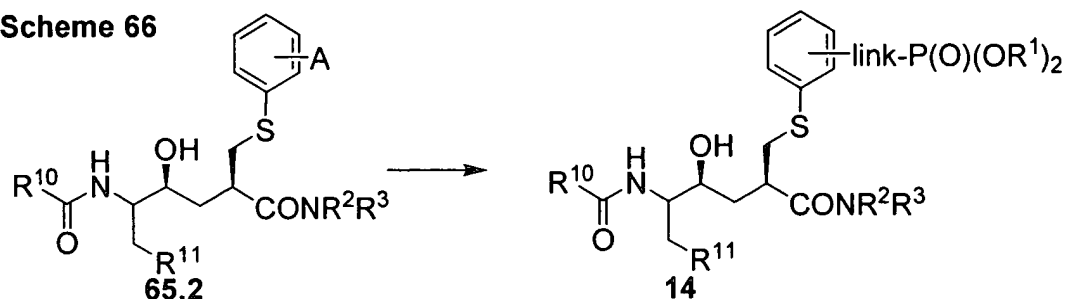
**Scheme 64**



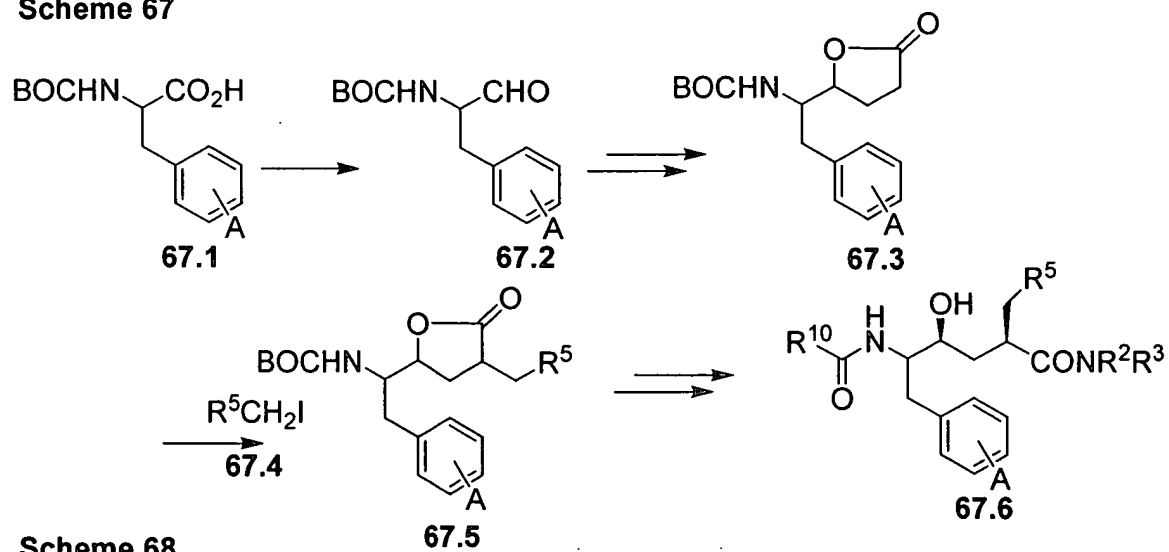
**Scheme 65**



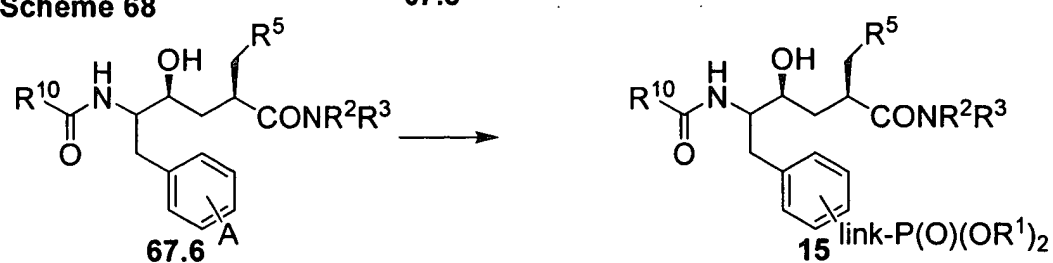
**Scheme 66**



**Scheme 67**



**Scheme 68**



**Preparation of the phosphonate ester intermediates 15 in which X is a direct bond and X' is sulfur.**

Schemes 69 and 70 illustrate the preparation of the phosphonate esters 15 in which X is a direct bond and X' is sulfur. In this procedure, the mesylate 51.1 is reacted, as described in Scheme 51, with the thiophenol derivative 69.1. The preparation of the thiophenol derivatives 69.1 is described below, Schemes 144 – 153. The product is then converted, as described in Scheme 51, into the corresponding aldehyde 69.3, and the latter compound is then transformed, as described in Scheme 49, into the lactone 69.4. The lactone is then alkylated, as described in Scheme 49, with the reagent  $R^5CH_2I$ , (67.4), to afford the alkylated product 69.5. This compound is then converted, as described in Scheme 49, into the diamide 69.6.

The reactions shown in Scheme 69 illustrate the preparation of the compounds 69.6 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 70 depicts the conversion of the compounds 69.6 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 15 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 69.6 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 15.

**Preparation of the phosphonate ester intermediates 15 in which X and X' are sulfur**

Schemes 71, 72 and 73 illustrate the preparation of the phosphonate esters 15 in which X and X' are sulfur. As shown in Scheme 71, the aldehyde 69.3 is converted, as described in Scheme 53, into the methylene lactone 71.1. The lactone is then reacted, as described in Scheme 53, with the thiol reagent 71.2 to yield the thioether product 71.3. The product is then transformed, as described in Scheme 53, into the diamide 71.4.

Scheme 72 illustrates an alternative method for the preparation of the diamide 71.4. In this procedure, the lactone 69.4 is reacted, as described in Scheme 54, with formaldehyde or a formaldehyde equivalent, to afford the hydroxymethyl product 72.1. The product is then transformed, by mesylation followed by reaction of the mesylate with the thiol reagent 71.2, using the procedures described in Scheme 53, into the thioether 71.3. The latter compound is then converted, as described in Scheme 53, into the diamide 71.4.

The reactions shown in Schemes 71 and 72 illustrate the preparation of the compounds 71.4 in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme 73 depicts the conversion of the compounds 71.4 in which A is [OH],

[SH], [NH], Br, into the phosphonate esters **15** in which X and X' are sulfur. In this procedure, the compounds **71.4** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **15**.

**Preparation of the phosphonate ester intermediates 15 in which X is sulfur and X' is a direct bond**

Schemes **74** and **75** illustrate the preparation of the phosphonate esters **15** in which X is sulfur and X' is a direct bond. In this procedure, the aldehyde **67.2** is converted, as described in Scheme **53**, into the methylene lactone **74.1**. The lactone is then reacted, as described in Scheme **53**, with the thiol **71.2** to afford the thioether **74.2**. This compound is then converted, as described in Scheme **53**, into the diamide **74.3**.

The reactions shown in Schemes **74** illustrate the preparation of the compounds **74.3** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **75** depicts the conversion of the compounds **74.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **74.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **15**.

**Preparation of the phosphonate ester intermediates 16 in which X and X' are direct bonds**

Schemes **76** and **77** illustrate the preparation of the phosphonate esters **16** in which X and X' are direct bonds. In this procedure, the lactone **49.6** is reacted, as described in Scheme **49**, with the iodo compound **67.4** to yield the alkylated lactone **76.1**. The lactone is then converted, as described in Scheme **49**, into the carboxylic acid **76.2**. The carboxylic acid is then coupled, as described in Scheme **1**, with the aminoindanol derivative **1.2** to afford the amide **76.3**. The latter compound is then converted, as described in Scheme **49**, into the diamide **76.4**.

The reactions shown in Scheme **76** illustrate the preparation of the compounds **76.4** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **77** depicts the conversion of the compounds **76.4** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X and X' are direct bonds. In this procedure, the compounds **76.4** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **16**.

**Preparation of the phosphonate ester intermediates 16 in which X is a direct bond and X' is sulfur**

Schemes 78 and 79 illustrate the preparation of the phosphonate esters 16 in which X is a direct bond and X' is sulfur. In this procedure, the lactone 54.1 is reacted, as described in Scheme 49, with the iodo compound 67.4, to produce the alkylated compound 78.1. This material is then transformed, as described in Scheme 49, into the carboxylic acid 78.2, which is then transformed, as described in Scheme 76, into the diamide 78.3.

The reactions shown in Scheme 78 illustrate the preparation of the compounds 78.3 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 79 depicts the conversion of the compounds 78.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 16 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 78.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 16.

**Preparation of the phosphonate ester intermediates 16 in which X and X' are sulfur**

Schemes 80, 81 and 82 illustrate the preparation of the phosphonate esters 15 in which X and X' are sulfur. As shown in Scheme 80, the methylene lactone 53.3 is reacted with the thiol 71.2 to produce the thioether 80.1. The compound is then transformed, as described in Scheme 49, into the silyl-protected carboxylic acid 80.2. This material is then converted, as described in Scheme 76, into the diamide 80.3.

Scheme 81 illustrates an alternative method for the preparation of the compounds 80.2. In this procedure, the mesylate 54.3 is reacted, as described in Scheme 54, with the thiol 71.2, to prepare the thioether 80.1. The product is then transformed, as described in Scheme 54, into the diamide 80.3.

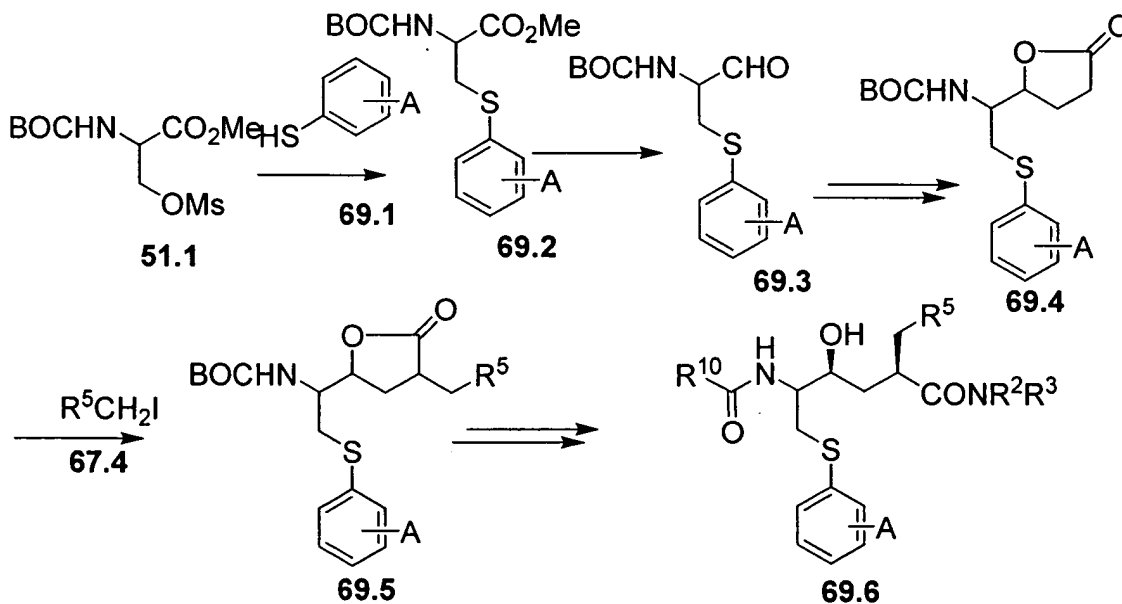
The reactions shown in Schemes 80 and 81 illustrate the preparation of the compounds 80.3 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 82 depicts the conversion of the compounds 80.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 16 in which X and X' are sulfur. In this procedure, the compounds 80.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 16.

**Preparation of the phosphonate ester intermediates 16 in which X is sulfur and X' is a direct bond**

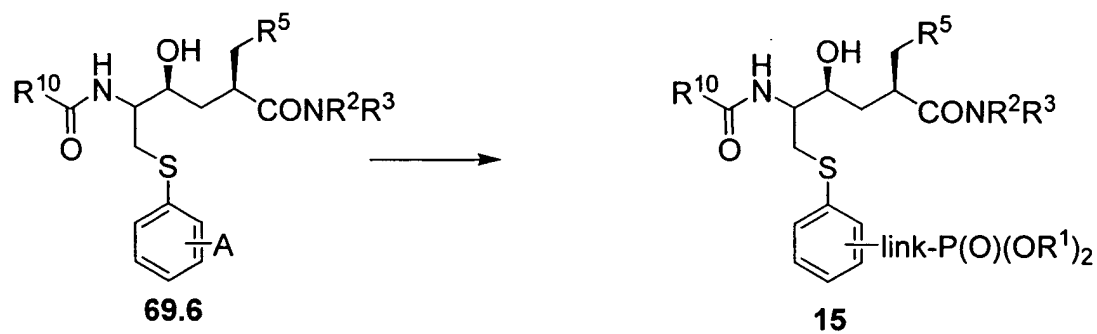
Schemes 83 and 84 illustrate the preparation of the phosphonate esters 16 in which X is sulfur and X' is a direct bond. In this procedure, the methylene lactone 53.3 is reacted, as described in Scheme 53, with the thiol 71.2 to yield the thioether 83.1. The product is then converted, as described in Scheme 76, into the diamide 83.2.

The reactions shown in Scheme 83 illustrate the preparation of the compounds 83.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 84 depicts the conversion of the compounds 83.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 16 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 83.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 16.

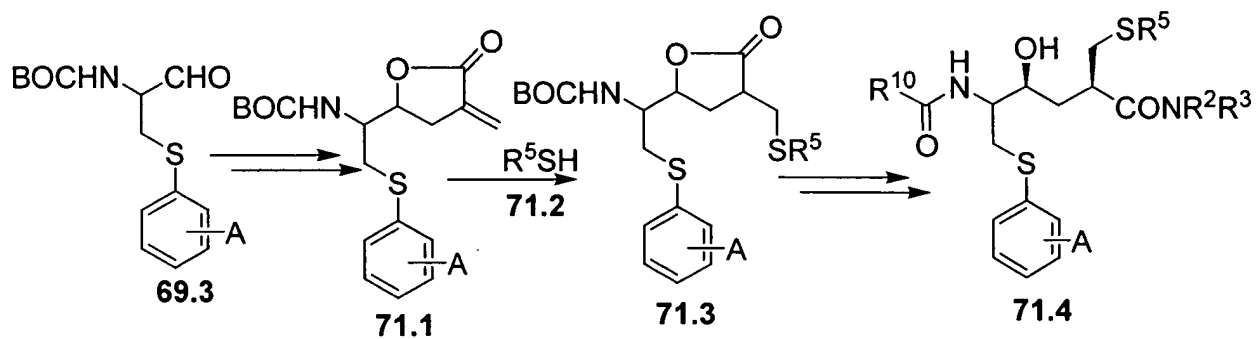
**Scheme 69**



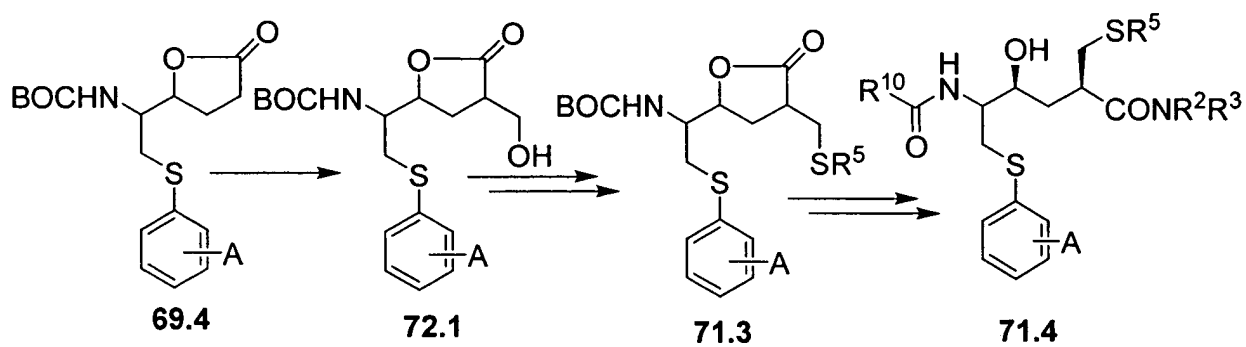
**Scheme 70**



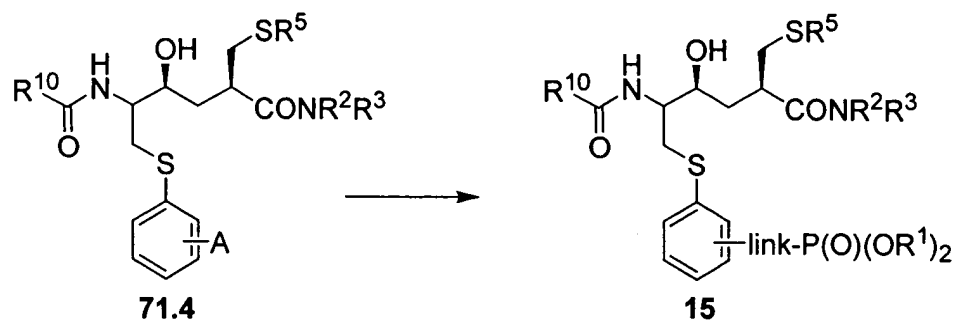
**Scheme 71**



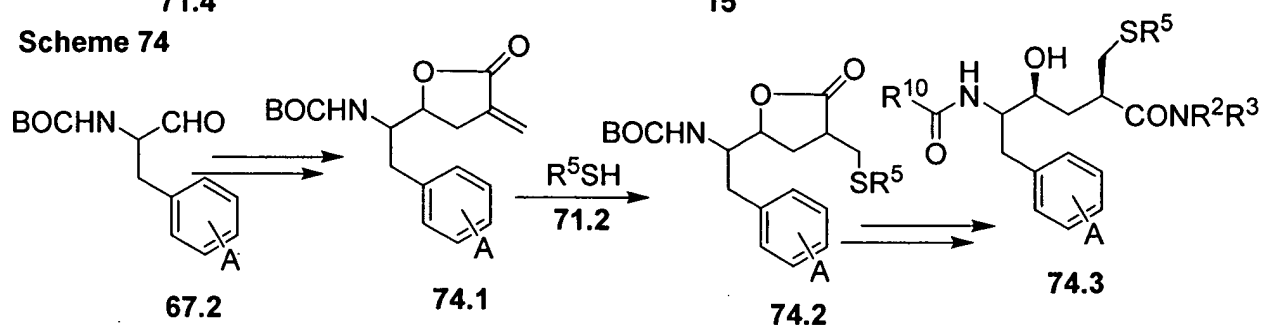
**Scheme 72**



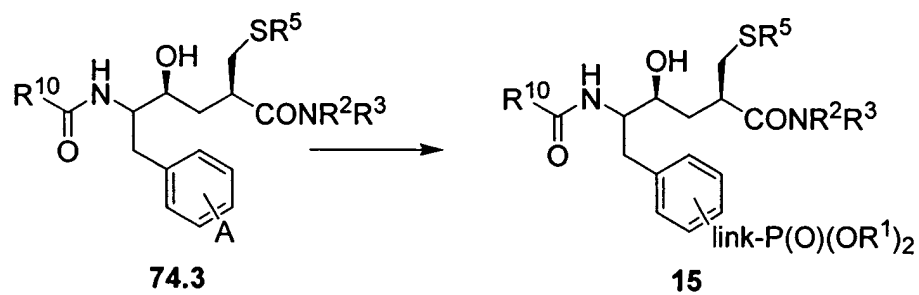
**Scheme 73**



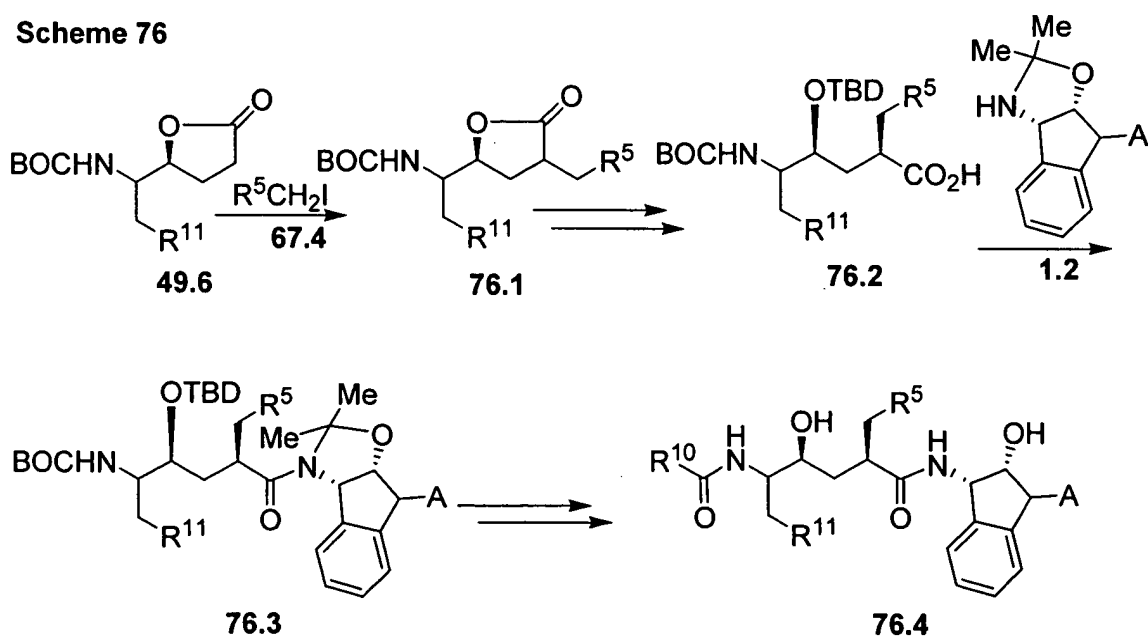
**Scheme 74**



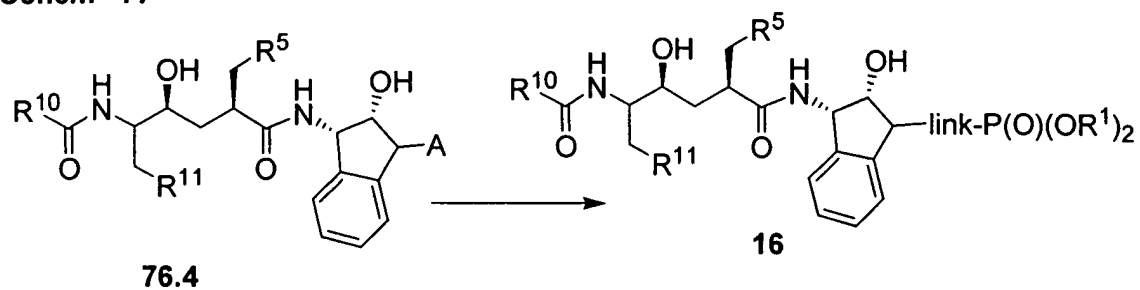
**Scheme 75**



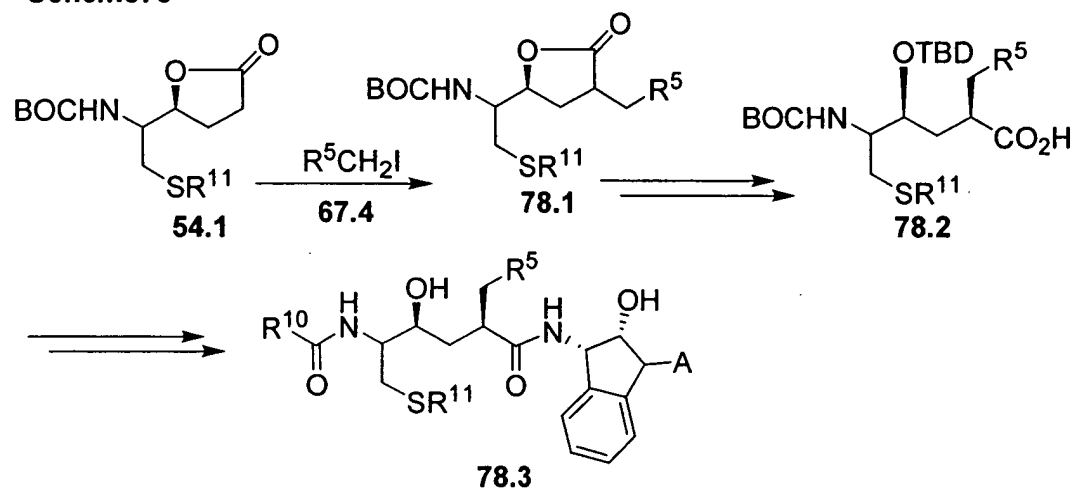
**Scheme 76**



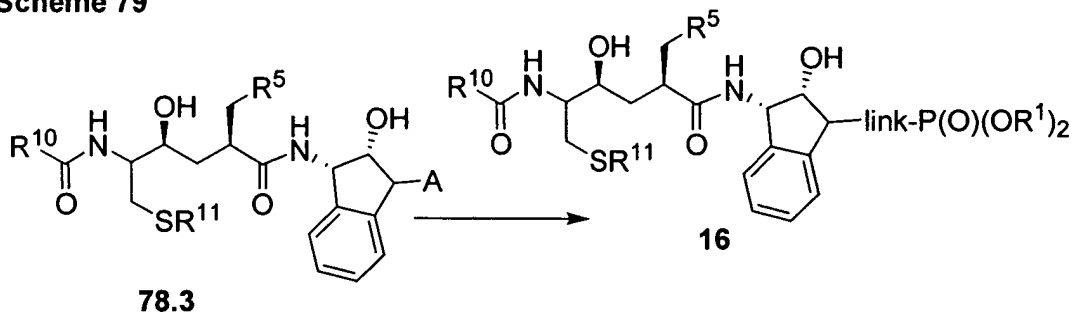
**Schem 77**



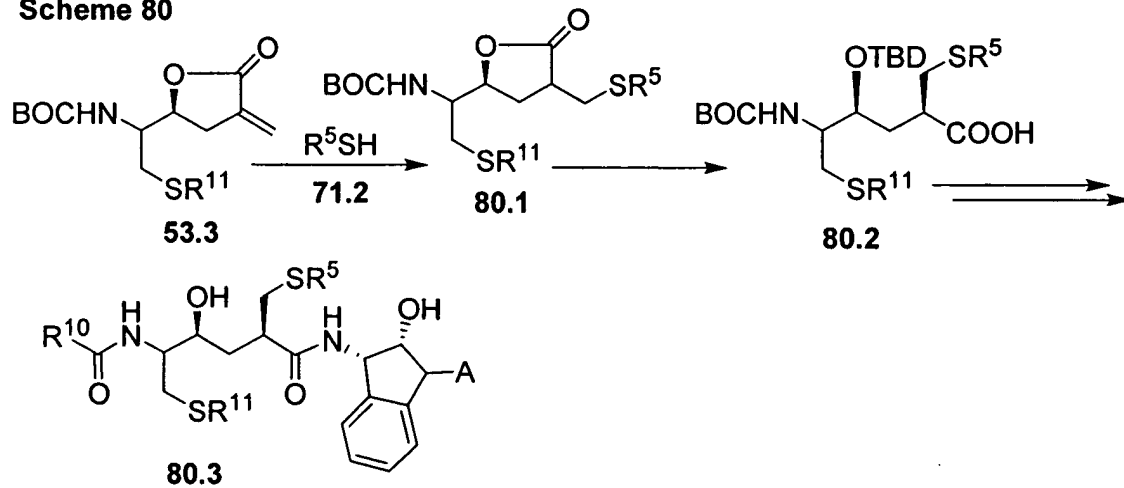
**Scheme78**



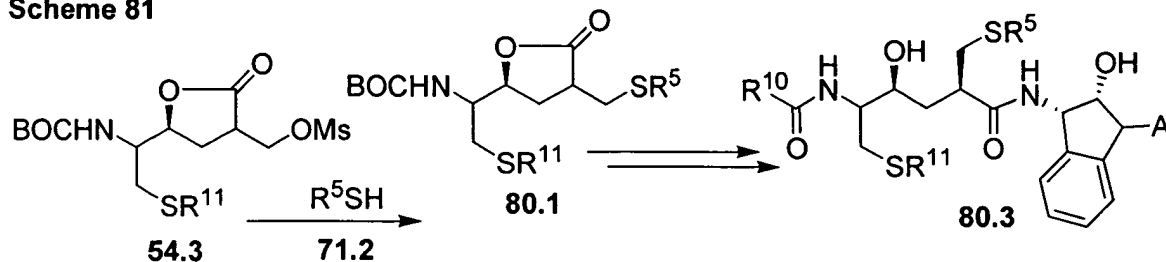
**Scheme 79**



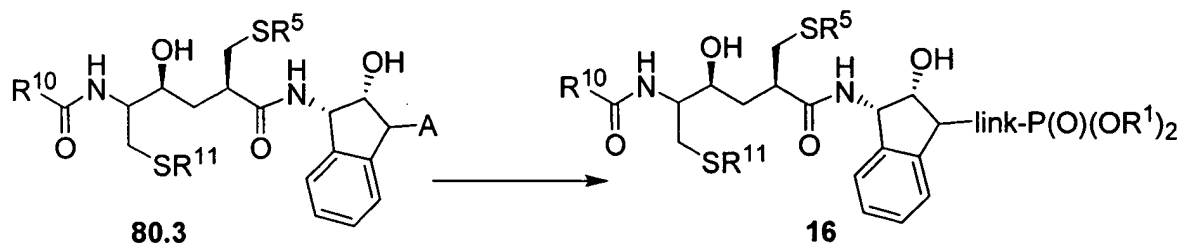
**Scheme 80**



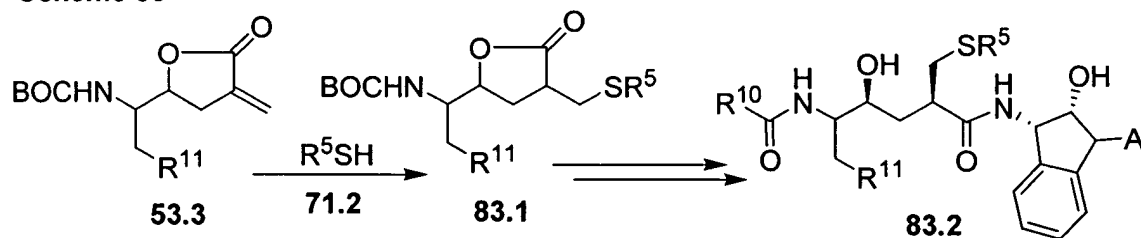
**Scheme 81**



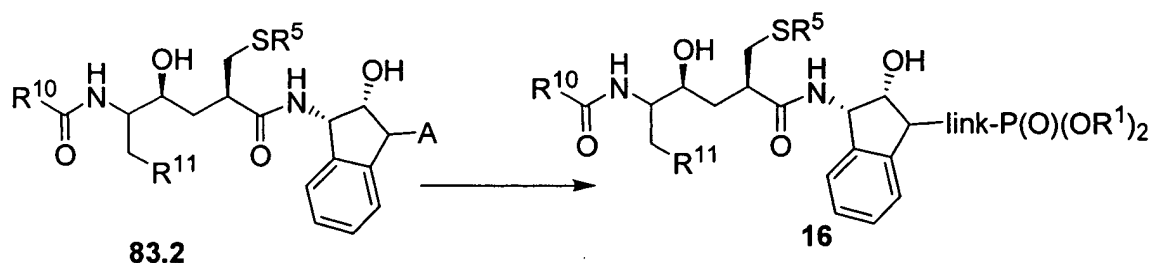
**Scheme 82**



**Scheme 83**



**Scheme 84**



#### Preparation of the phosphonate ester intermediates **17** in which X and X' are direct bonds

Schemes **85** and **86** illustrate the preparation of the phosphonate esters **17** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the aminochroman derivative **33.1** to afford the amide **85.1**. The product is then converted, as described in Scheme **49**, into the diamide **85.2**.

The reactions shown in Scheme **85** illustrate the preparation of the compounds **85.2** in which the substituent A is either the group  $\text{link-P(O)(OR}^1)_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme **86** depicts the conversion of the compounds **85.2** in which A is [OH], [SH],

[NH], Br, into the phosphonate esters **17** in which X and X' are direct bonds. In this procedure, the compounds **85.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **17**.

**Preparation of the phosphonate ester intermediates **17** in which X is a direct bond and X' is sulfur**

Schemes **87** and **88** illustrate the preparation of the phosphonate esters **17** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled with the amine **33.1** to afford the amide **87.1**. The product is then converted, as described in Scheme **49**, into the diamide **87.2**.

The reactions shown in Scheme **87** illustrate the preparation of the compounds **87.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **88** depicts the conversion of the compounds **87.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **87.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **17**.

**Preparation of the phosphonate ester intermediates **17** in which X and X' are sulfur**

Schemes **89** and **90** illustrate the preparation of the phosphonate esters **17** in which X and X' are sulfur. As shown in Scheme **89**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the chroman amine **33.1** to give the amide **89.1**. The product is then transformed, as described in Scheme **49**, into the diamide **89.2**.

The reactions shown in Scheme **89** illustrate the preparation of the compounds **89.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **90** depicts the conversion of the compounds **89.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X and X' are sulfur. In this procedure, the compounds **89.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **17**.

**Preparation of the phosphonate ester intermediates **17** in which X is sulfur and X' is a direct bond**

Schemes **91** and **92** illustrate the preparation of the phosphonate esters **17** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1**, which is an

intermediate compound in the conversion of the lactone **83.1** into the diamide **83.2**, (Scheme **83**), is coupled, as described in Scheme **1**, with the chroman amine **33.1** to afford the amide **91.2**. The product is then converted, as described in Scheme **49**, into the diamide **91.3**.

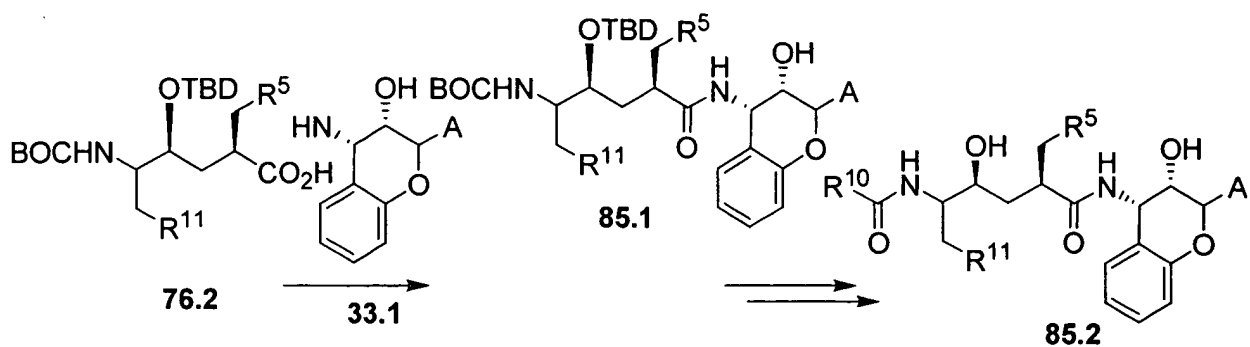
The reactions shown in Scheme **91** illustrate the preparation of the compounds **91.3** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **92** depicts the conversion of the compounds **91.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **91.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **17**.

#### **Preparation of the phosphonate ester intermediates 18 in which X and X' are direct bonds**

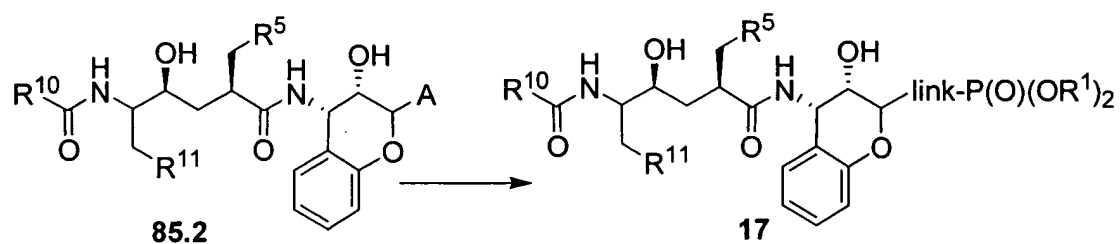
Schemes **93** and **94** illustrate the preparation of the phosphonate esters **18** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the ethanolamine derivative **29.1** to afford the amide **93.1**. The product is then converted, as described in Scheme **49**, into the diamide **93.2**.

The reactions shown in Scheme **93** illustrate the preparation of the compounds **93.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **94** depicts the conversion of the compounds **93.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **18** in which X and X' are direct bonds. In this procedure, the compounds **93.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **18**.

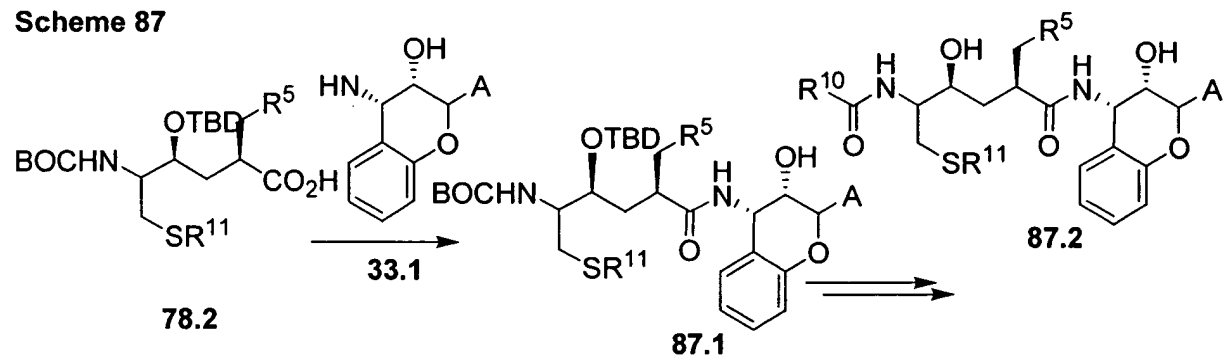
**Scheme 85**



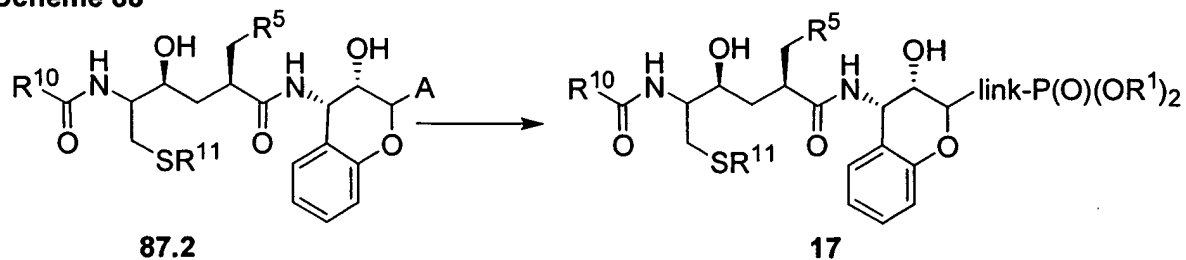
**Scheme 86**



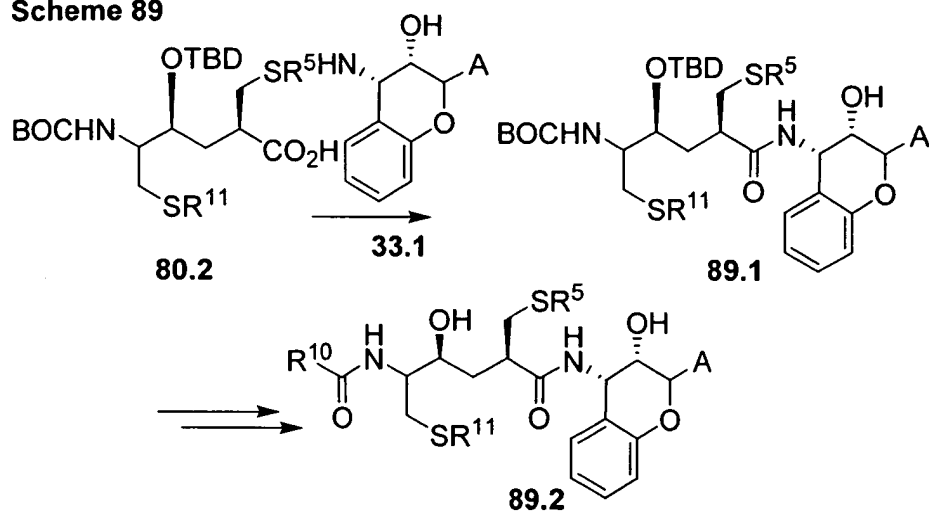
**Scheme 87**



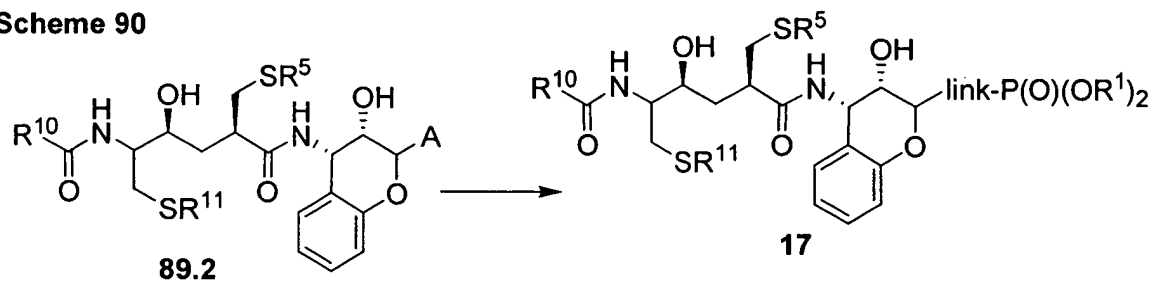
**Scheme 88**



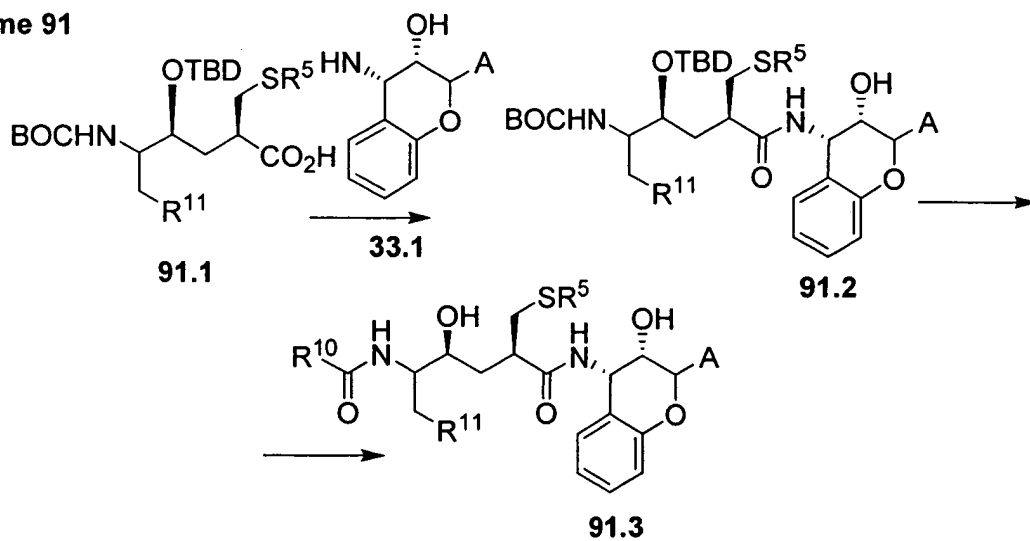
**Scheme 89**



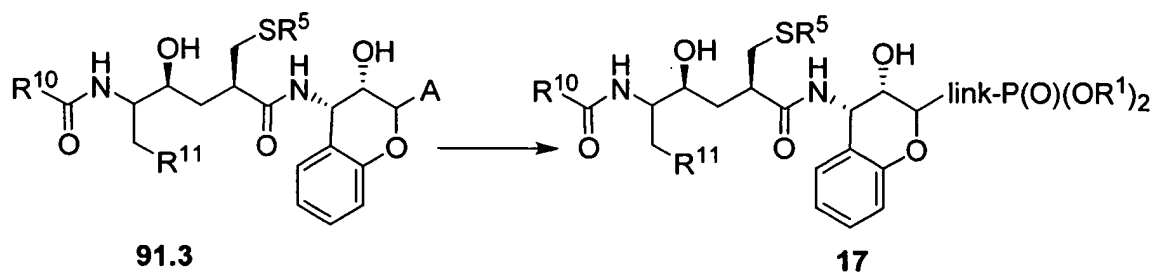
**Scheme 90**



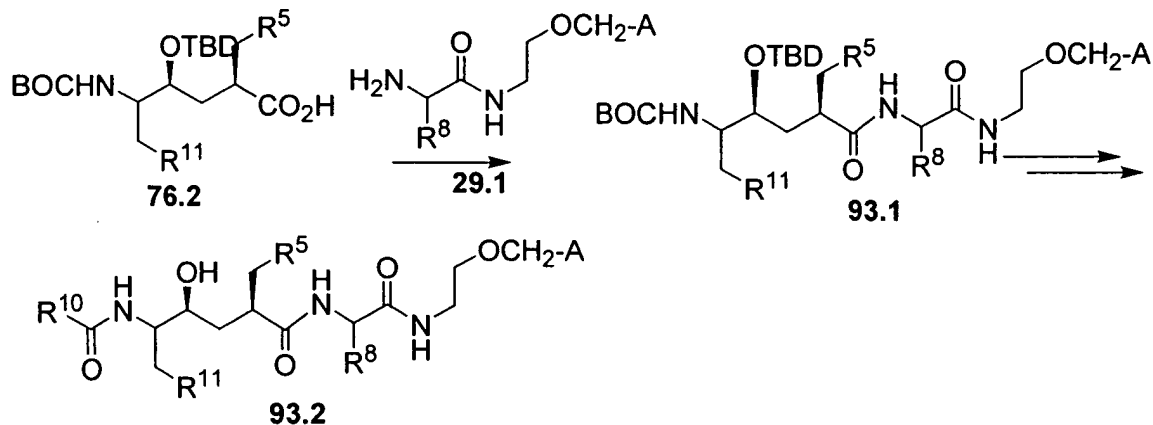
**Scheme 91**



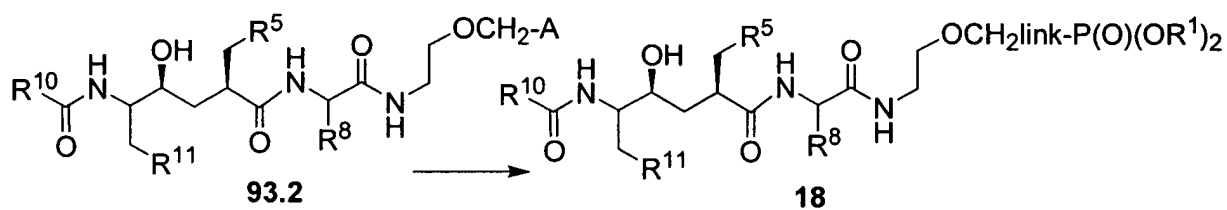
**Scheme 92**



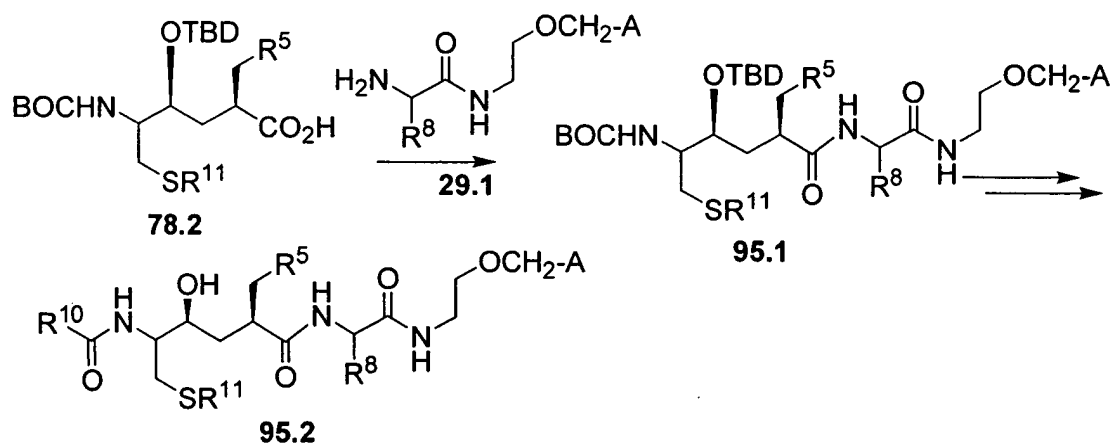
**Scheme 93**



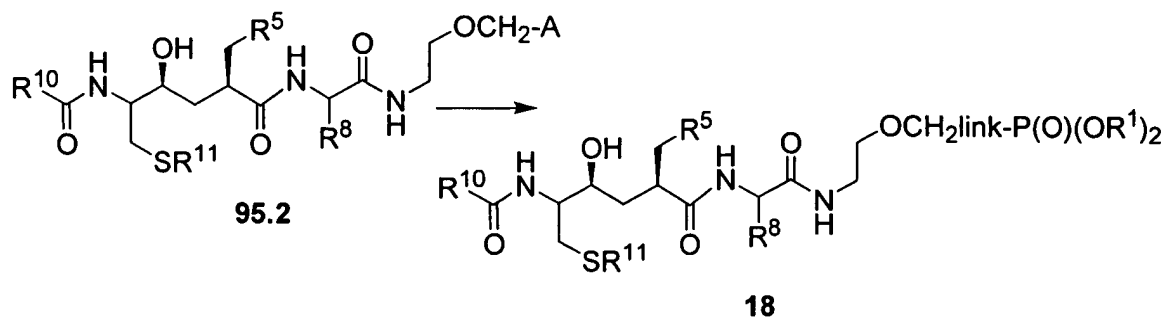
**Scheme 94**



**Scheme 95**



**Scheme 96**



### **Preparation of the phosphonate ester intermediates 18 in which X and X' are sulfur**

Schemes 97 and 98 illustrate the preparation of the phosphonate esters 18 in which X and X' are sulfur. As shown in Scheme 97, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the ethanolamine derivative 29.1 to give the amide 97.1. The product is then transformed, as described in Scheme 49, into the diamide 97.2.

The reactions shown in Scheme 97 illustrate the preparation of the compounds 97.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 98 depicts the conversion of the compounds 97.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 18 in which X and X' are sulfur. In this procedure, the compounds 97.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 18.

### **Preparation of the phosphonate ester intermediates 18 in which X is sulfur and X' is a direct bond**

Schemes 99 and 100 illustrate the preparation of the phosphonate esters 18 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the ethanolamine derivative 29.1 to afford the amide 99.1. The product is then converted, as described in Scheme 49, into the diamide 99.2.

The reactions shown in Scheme 99 illustrate the preparation of the compounds 99.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 100 depicts the conversion of the compounds 99.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 18 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 99.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 18.

### **Preparation of the phosphonate ester intermediates 19 in which X and X' are direct bonds**

Schemes 101 and 102 illustrate the preparation of the phosphonate esters 19 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 1, with the phenylalanine derivative 37.1 to afford the amide 101.1. The product is then converted, as described in Scheme 49, into the diamide 101.2.

The reactions shown in Scheme 101 illustrate the preparation of the compounds 101.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH],

[NH], Br. Scheme 102 depicts the conversion of the compounds 101.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X and X' are direct bonds. In this procedure, the compounds 101.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 19.

**Preparation of the phosphonate ester intermediates 19 in which X is a direct bond and X' is sulfur**

Schemes 103 and 104 illustrate the preparation of the phosphonate esters 19 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as described in Scheme 1, with the amine 37.1 to afford the amide 103.1. The product is then converted, as described in Scheme 49, into the diamide 103.2.

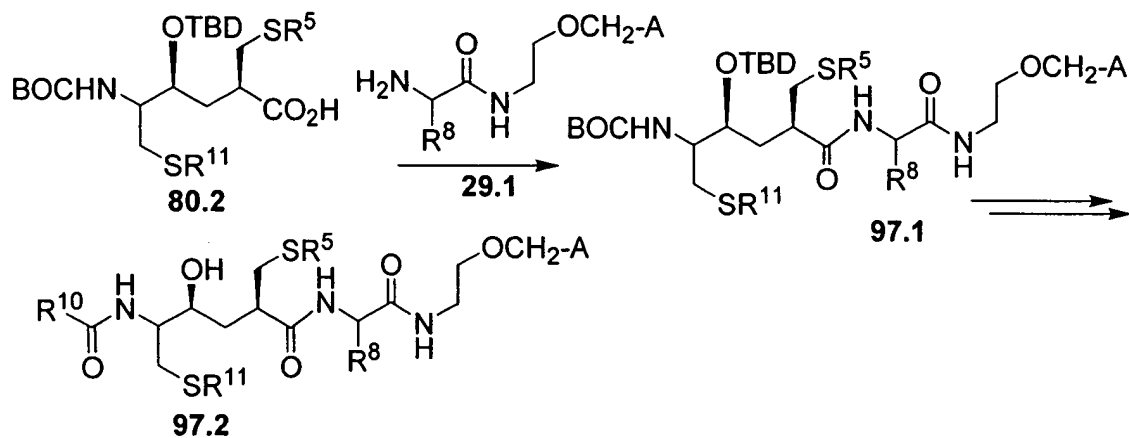
The reactions shown in Scheme 103 illustrate the preparation of the compounds 103.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 104 depicts the conversion of the compounds 103.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 103.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 19.

**Preparation of the phosphonate ester intermediates 19 in which X and X' are sulfur**

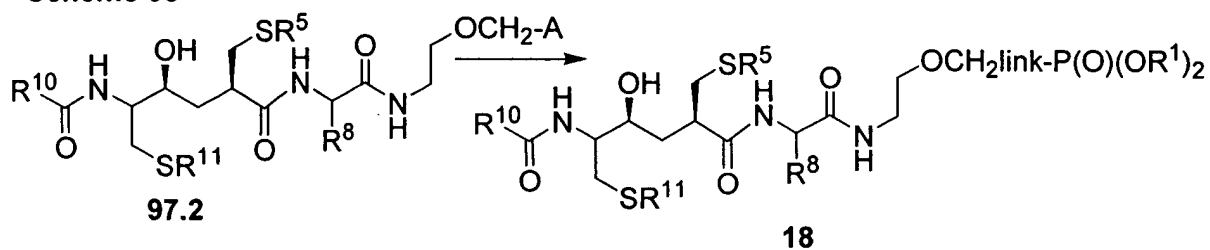
Schemes 105 and 106 illustrate the preparation of the phosphonate esters 19 in which X and X' are sulfur. As shown in Scheme 105, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the phenylalanine derivative 37.1 to give the amide 105.1. The product is then transformed, as described in Scheme 49, into the diamide 105.2.

The reactions shown in Scheme 105 illustrate the preparation of the compounds 105.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 106 depicts the conversion of the compounds 105.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X and X' are sulfur. In this procedure, the compounds 105.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 19.

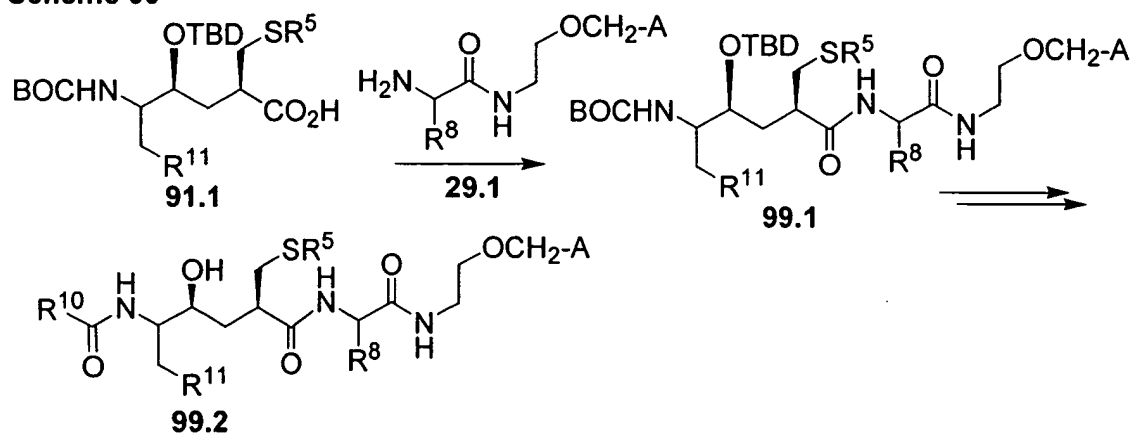
**Schem 97**



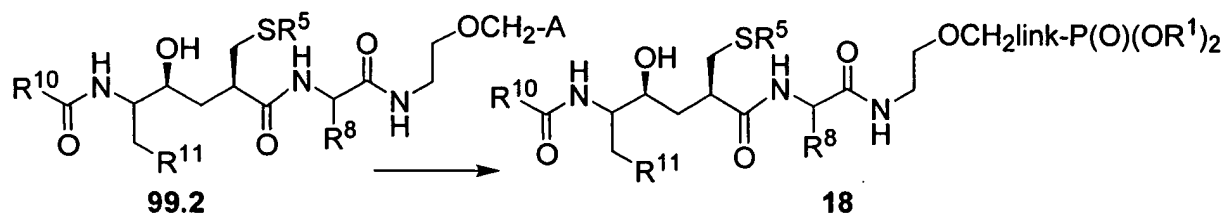
**Scheme 98**



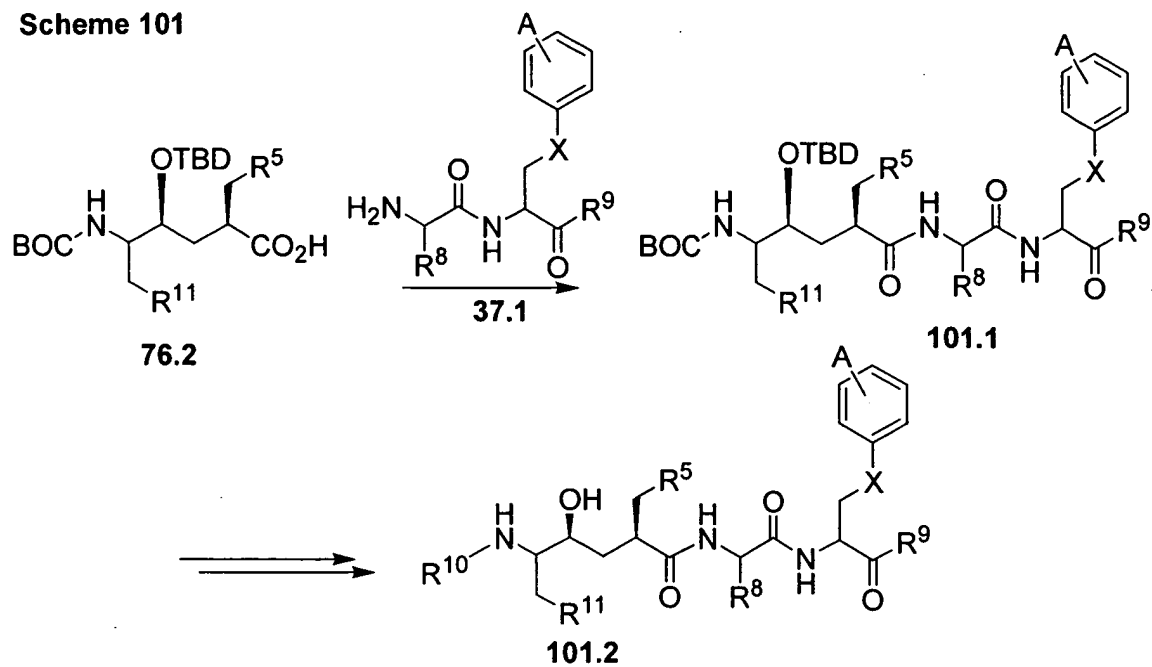
**Scheme 99**



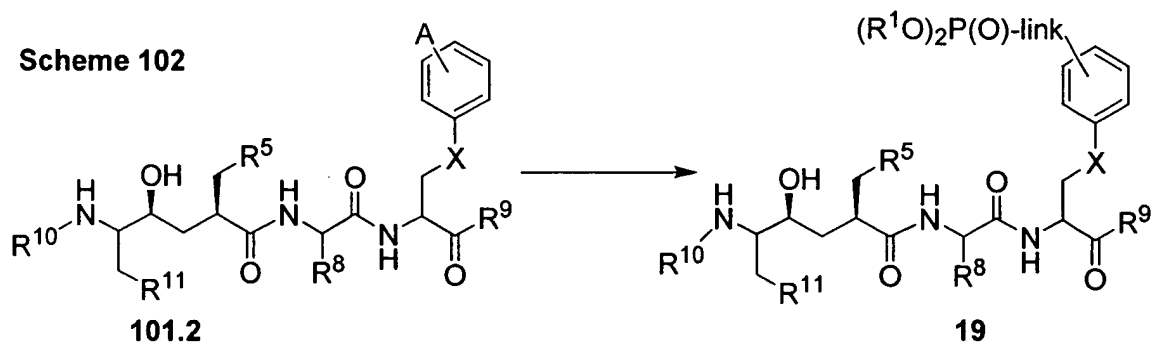
**Scheme 100**



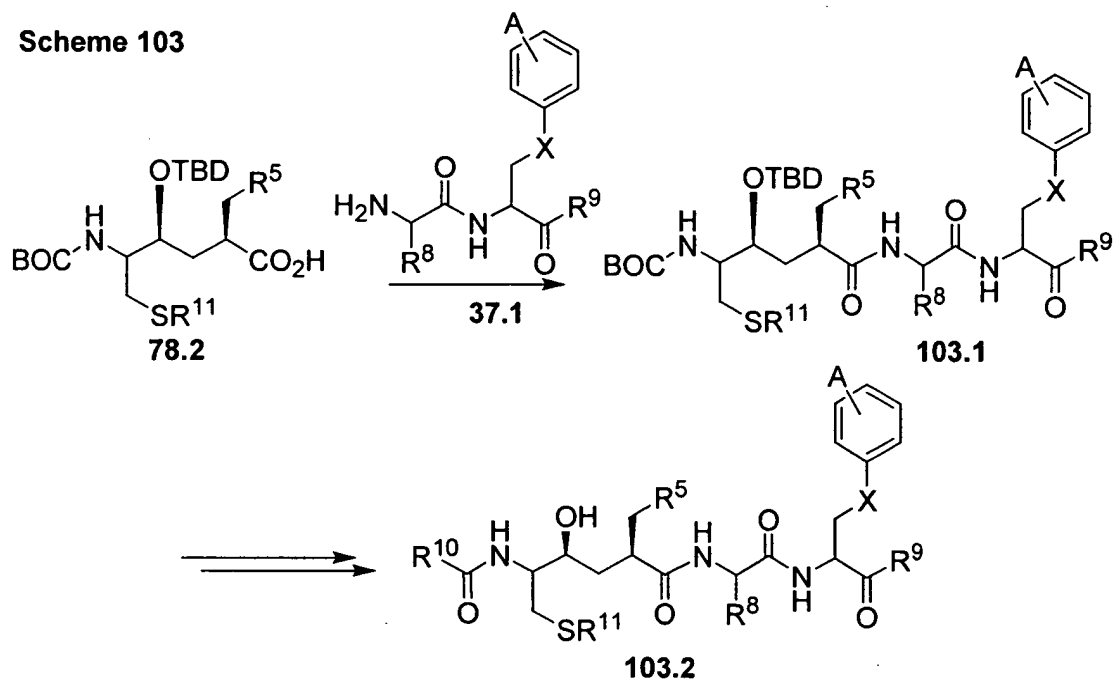
**Scheme 101**



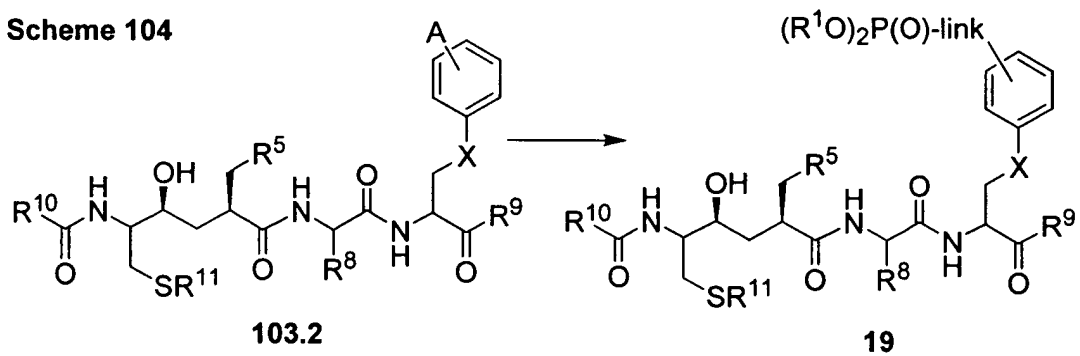
**Scheme 102**



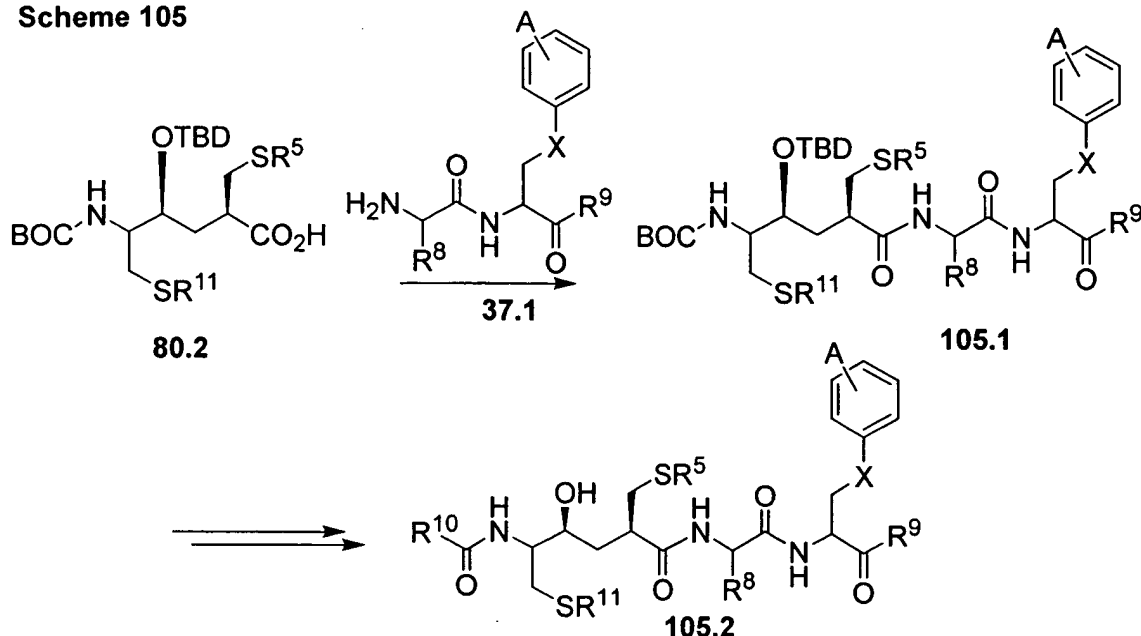
**Scheme 103**



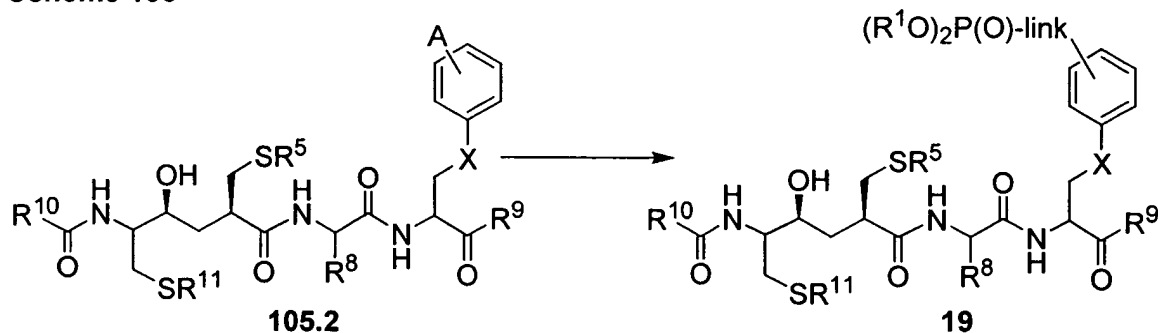
**Scheme 104**



**Scheme 105**



**Scheme 106**



**Preparation of the phosphonate ester intermediates 19 in which X is sulfur and X' is a direct bond**

Schemes 107 and 108 illustrate the preparation of the phosphonate esters 19 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the phenylalanine derivative 37.1 to afford the amide 107.1. The product is then converted, as described in Scheme 49, into the diamide 107.2.

The reactions shown in Scheme 107 illustrate the preparation of the compounds 107.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 108 depicts the conversion of the compounds 107.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X is sulfur and X' is a direct bond. In this

procedure, the compounds **107.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **19**.

**Preparation of the phosphonate ester intermediates 20 in which X and X' are direct bonds**

Schemes **109** and **110** illustrate the preparation of the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to afford the amide **109.1**. The product is then converted, as described in Scheme **49**, into the diamide **109.2**.

The reactions shown in Scheme **109** illustrate the preparation of the compounds **109.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **110** depicts the conversion of the compounds **109.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the compounds **109.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **20**.

**Preparation of the phosphonate ester intermediates 20 in which X is a direct bond and X' is sulfur**

Schemes **111** and **112** illustrate the preparation of the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **41.1** to afford the amide **111.1**. The product is then converted, as described in Scheme **49**, into the diamide **111.2**.

The reactions shown in Scheme **111** illustrate the preparation of the compounds **111.2** in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme **112** depicts the conversion of the compounds **111.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **111.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **20**.

**Preparation of the phosphonate ester intermediates 20 in which X and X' are sulfur**

Schemes **113** and **114** illustrate the preparation of the phosphonate esters **20** in which X and X' are sulfur. As shown in Scheme **113**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to give the amide **113.1**. The product is then transformed, as described in Scheme **49**, into the diamide **113.2**.

The reactions shown in Scheme 113 illustrate the preparation of the compounds 113.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 114 depicts the conversion of the compounds 113.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 20 in which X and X' are sulfur. In this procedure, the compounds 113.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 20.

**Preparation of the phosphonate ester intermediates 20 in which X is sulfur and X' is a direct bond**

Schemes 115 and 116 illustrate the preparation of the phosphonate esters 20 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the tert. butylamine derivative 41.1 to afford the amide 115.1. The product is then converted, as described in Scheme 49, into the diamide 115.2.

The reactions shown in Scheme 115 illustrate the preparation of the compounds 115.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 116 depicts the conversion of the compounds 115.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 20 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 115.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 20.

**Preparation of the phosphonate ester intermediates 21 in which X and X' are direct bonds**

Schemes 117 and 118 illustrate the preparation of the phosphonate esters 21 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 1, with the decahydroisoquinoline derivative 45.1 to afford the amide 117.1. The product is then converted, as described in Scheme 49, into the diamide 117.2.

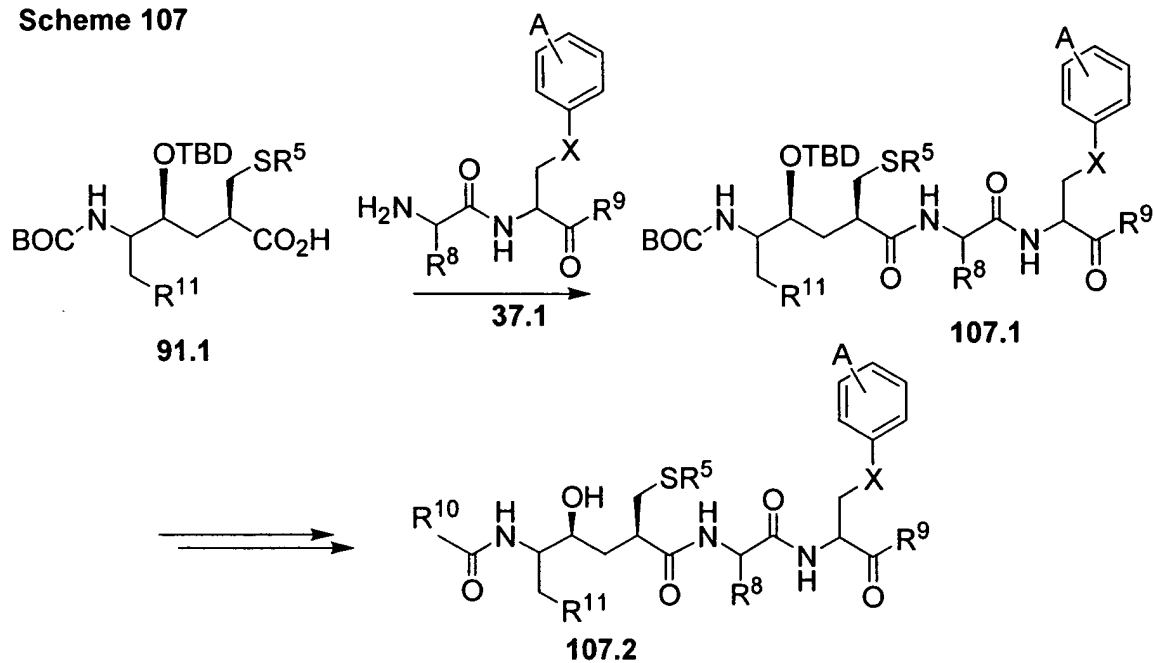
The reactions shown in Scheme 117 illustrate the preparation of the compounds 117.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 118 depicts the conversion of the compounds 117.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X and X' are direct bonds. In this procedure, the compounds 117.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

**Preparation of the phosphonate ester intermediates 21 in which X is a direct bond and X' is sulfur**

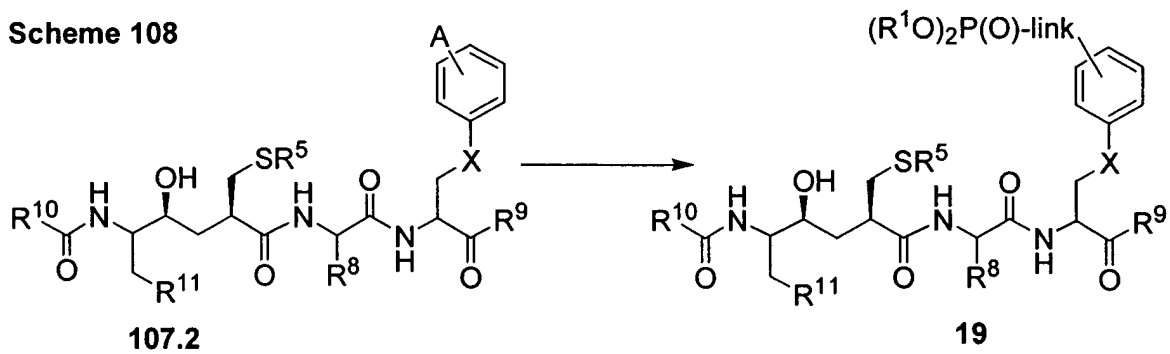
Schemes 119 and 120 illustrate the preparation of the phosphonate esters 21 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as described in Scheme 1, with the amine 45.1 to afford the amide 119.1. The product is then converted, as described in Scheme 49, into the diamide 119.2.

The reactions shown in Scheme 119 illustrate the preparation of the compounds 119.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 120 depicts the conversion of the compounds 119.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 119.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

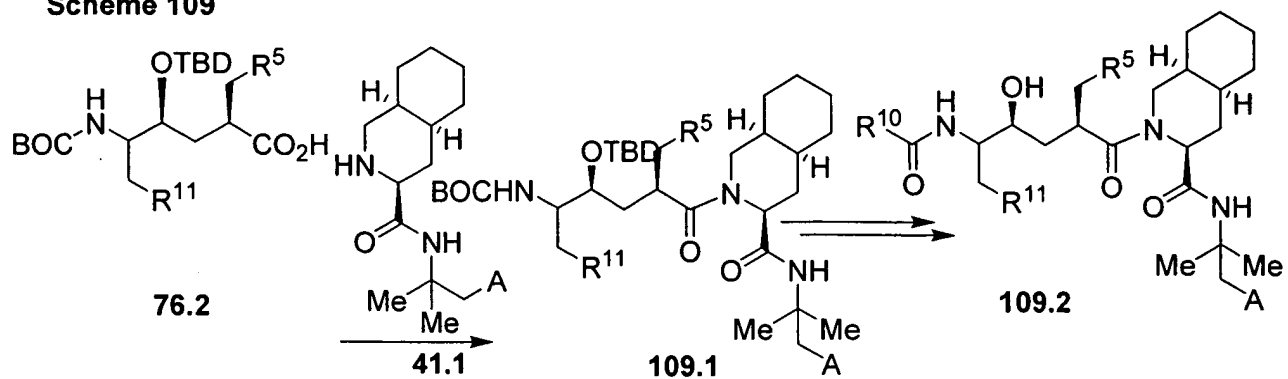
**Scheme 107**



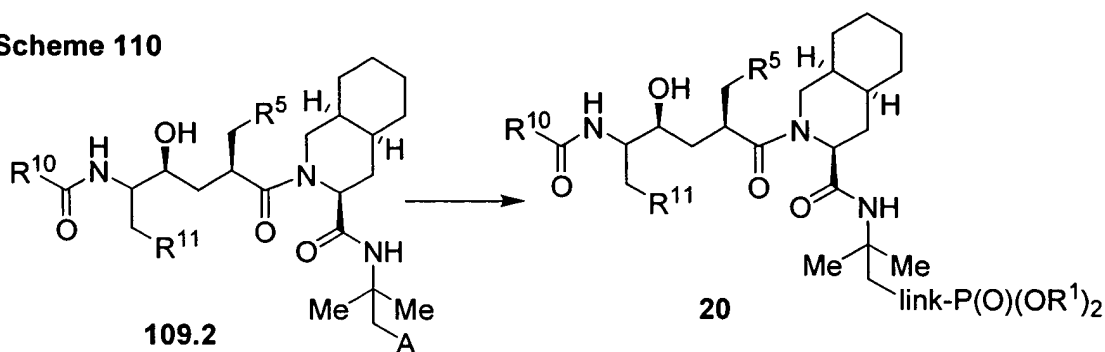
**Scheme 108**



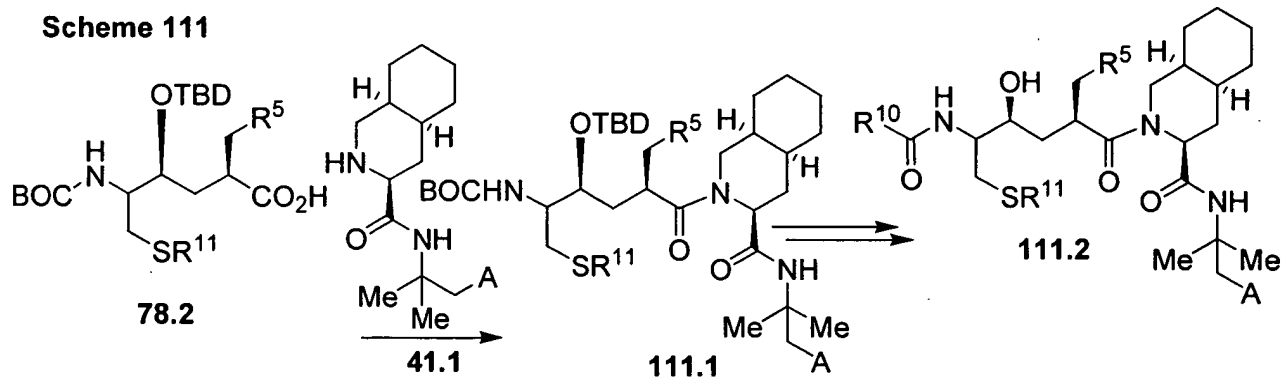
**Scheme 109**



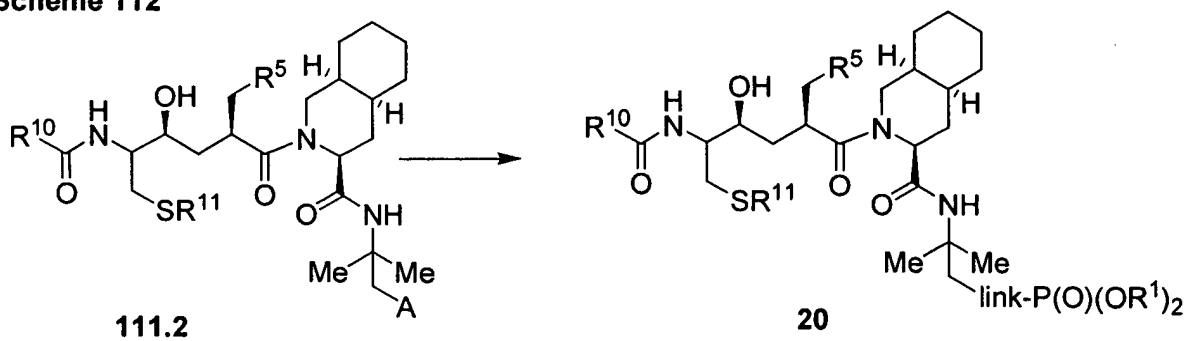
**Scheme 110**



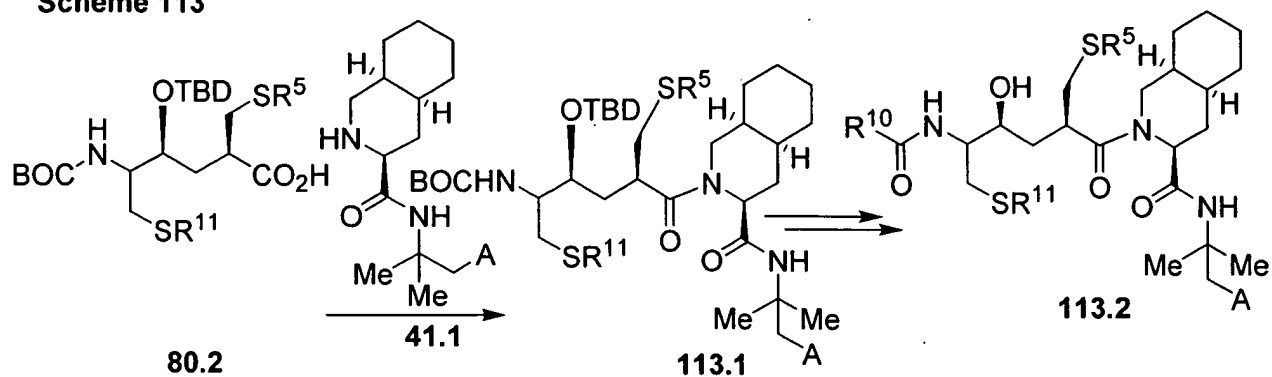
**Scheme 111**



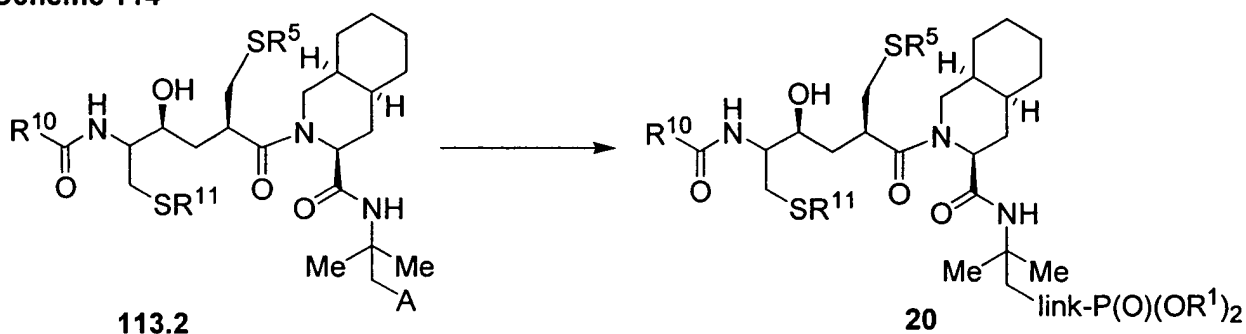
**Scheme 112**



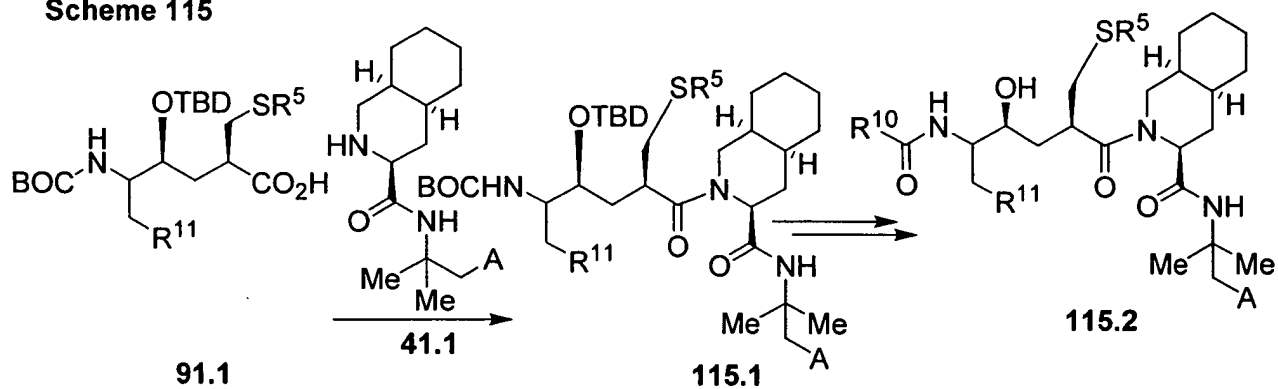
**Scheme 113**



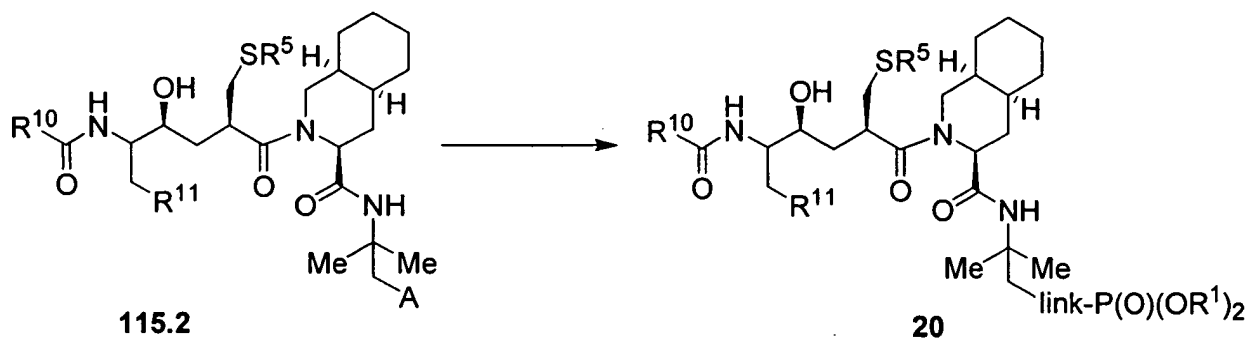
**Scheme 114**



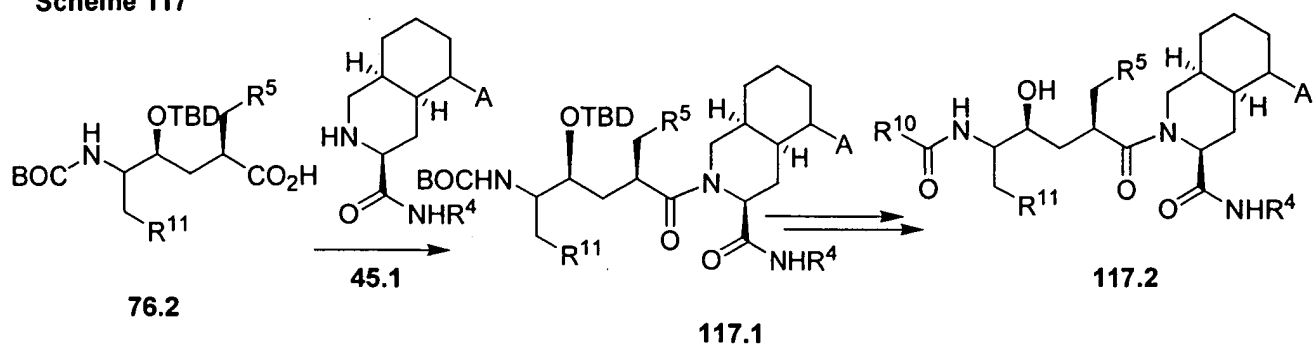
**Scheme 115**



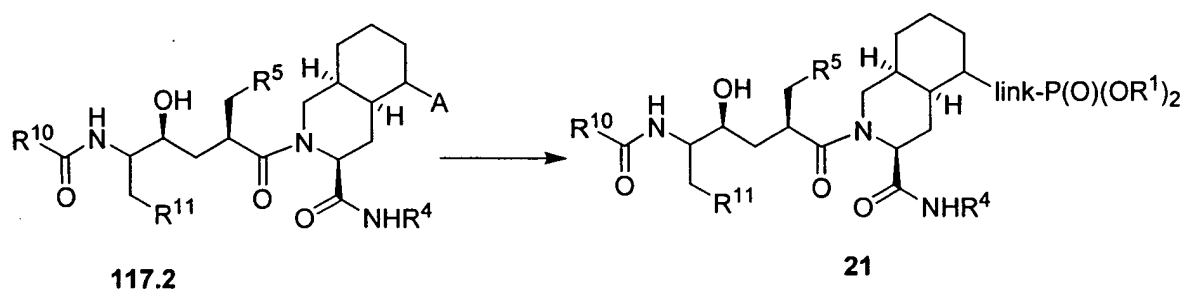
**Scheme 116**



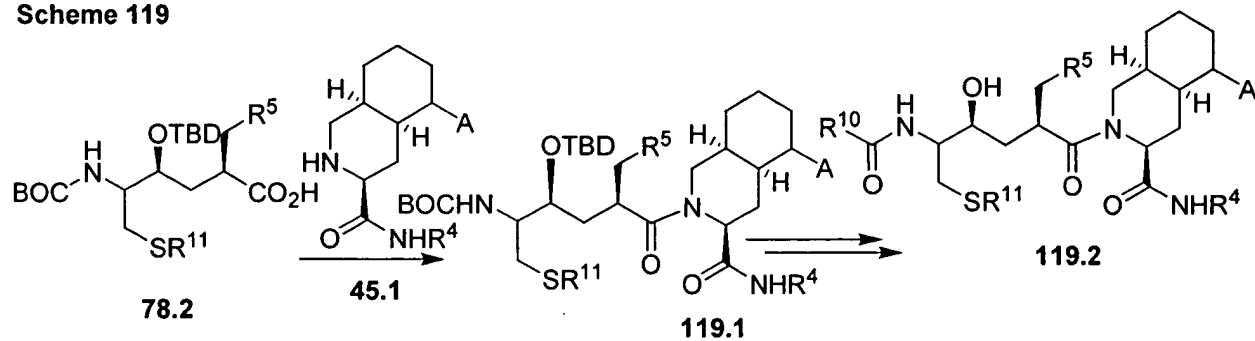
**Scheme 117**



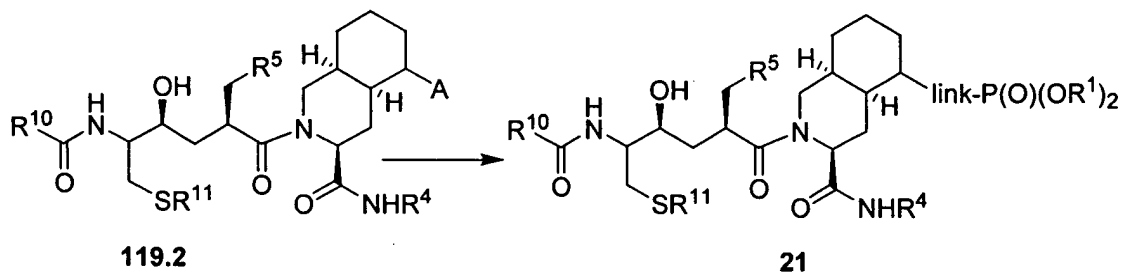
**Scheme 118**



**Scheme 119**



**Scheme 120**



### **Preparation of the phosphonate ester intermediates 21 in which X and X' are sulfur**

Schemes 121 and 122 illustrate the preparation of the phosphonate esters 21 in which X and X' are sulfur. As shown in Scheme 121, the carboxylic acid 80.2 is coupled with the amine 45.1 to give the amide 121.1. The product is then transformed, as described in Scheme 49, into the diamide 121.2.

The reactions shown in Scheme 121 illustrate the preparation of the compounds 121.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 122 depicts the conversion of the compounds 121.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X and X' are sulfur. In this procedure, the compounds 121.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

### **Preparation of the phosphonate ester intermediates 21 in which X is sulfur and X' is a direct bond**

Schemes 123 and 124 illustrate the preparation of the phosphonate esters 21 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the amine 45.1 to afford the amide 123.1. The product is then converted, as described in Scheme 49, into the diamide 123.2.

The reactions shown in Schemes 123 illustrate the preparation of the compounds 123.2 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 124 depicts the conversion of the compounds 123.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 123.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

### **Preparation of the phosphonate ester intermediates 22 in which X and X' are direct bonds**

Schemes 125 and 126 illustrate the preparation of the phosphonate esters 22 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 5 with the amine 1.6, to afford the amide 125.1. The BOC protecting group is then removed, as described in Scheme 49, to yield the amine 125.2. The latter compound is then coupled with the carboxylic acid 125.3 to produce the amide 125.4. The preparation of the carboxylic acid reactant 125.3 is described in Scheme 191.

The reactions shown in Scheme 125 illustrate the preparation of the compounds 125.4 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 126 depicts the conversion of the compounds 125.4 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22 in which X and X' are direct bonds. In this procedure, the compounds 125.4 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22

**Preparation of the phosphonate ester intermediates 22 in which X is a direct bond and X' is sulfur**

Schemes 127 and 128 illustrate the preparation of the phosphonate esters 22 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as described in Scheme 5 with the amine 1.6, to afford the amide 127.1. The BOC protecting group is then removed, as described in Scheme 49, to yield the amine 127.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 127.3.

The reactions shown in Scheme 127 illustrate the preparation of the compounds 127.3 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 128 depicts the conversion of the compounds 127.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22, in which X is a direct bond and X' is sulfur. In this procedure, the compounds 127.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

**Preparation of the phosphonate ester intermediates 22 in which X and X' are sulfur**

Schemes 129 and 130 illustrate the preparation of the phosphonate esters 22 in which X and X' are sulfur. As shown in Scheme 129, the carboxylic acid 80.2 is coupled, as described in Scheme 5, with the amine 1.6, to afford the amide 129.1. The BOC protecting group is then removed, as described in Scheme 49, to yield the amine 129.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 129.3.

The reactions shown in Scheme 129 illustrate the preparation of the compounds 129.3 in which the substituent A is either the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor such as [OH], [SH], [NH], Br. Scheme 130 depicts the conversion of the compounds 129.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22, in which X and X' are sulfur. In this procedure,

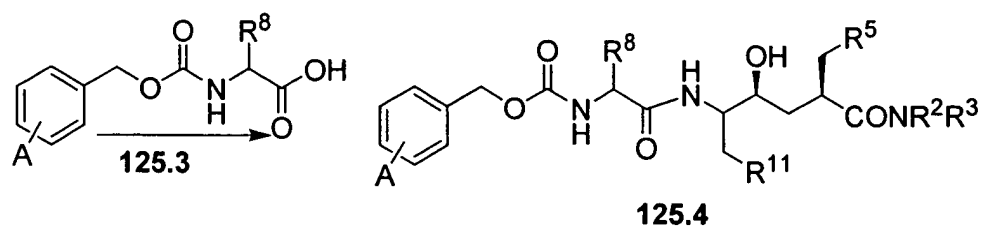
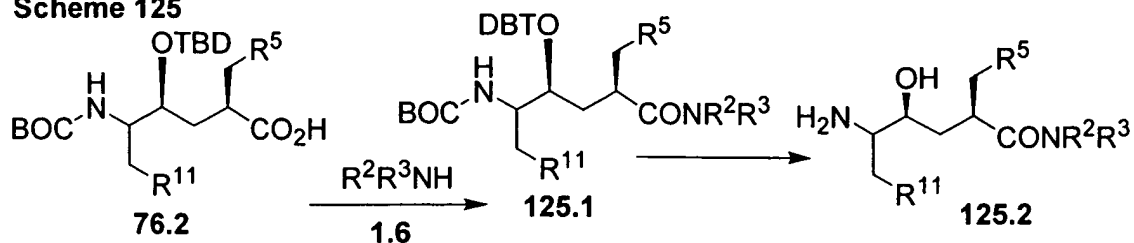
the compounds **129.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **22**.

**Preparation of the phosphonate ester intermediates **22** in which X is sulfur and X' is a direct bond**

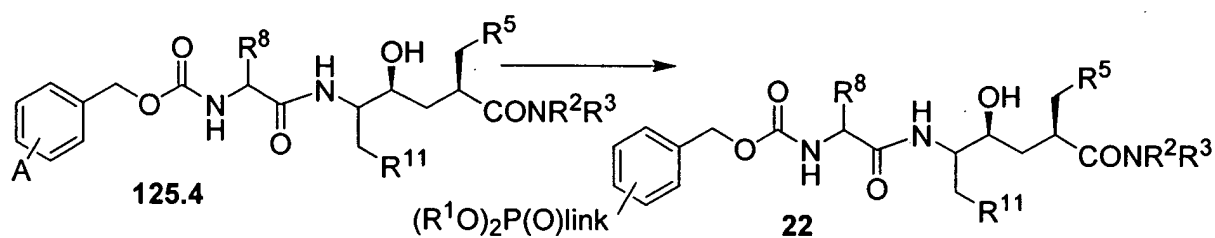
Schemes **131** and **132** illustrate the preparation of the phosphonate esters **22** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **5**, with the amine **1.6**, to afford the amide **131.1**. The BOC protecting group is then removed, as described in Scheme **49**, to yield the amine **131.2**. The latter compound is then coupled, as described in Scheme **1**, with the carboxylic acid **125.3** to produce the amide **131.3**.

The reactions shown in Scheme **131** illustrate the preparation of the compounds **131.3** in which the substituent A is either the group  $\text{link-P(O)(OR}^1\text{)}_2$  or a precursor such as [OH], [SH], [NH], Br. Scheme **132** depicts the conversion of the compounds **131.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **22** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **131.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **22**.

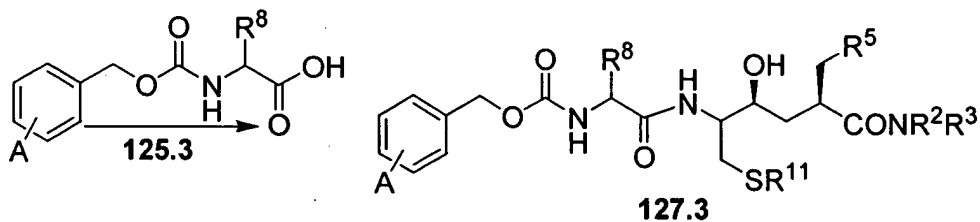
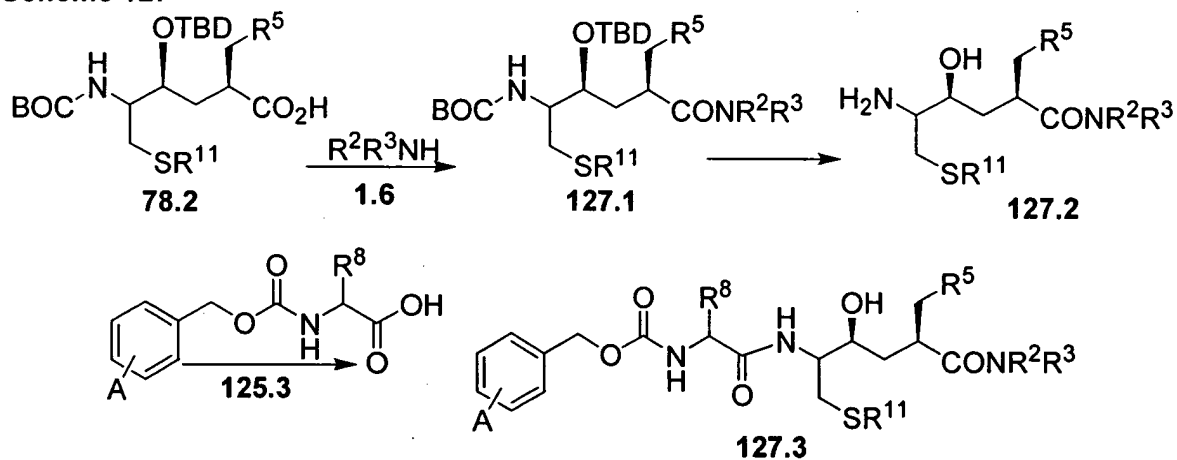
**Scheme 125**



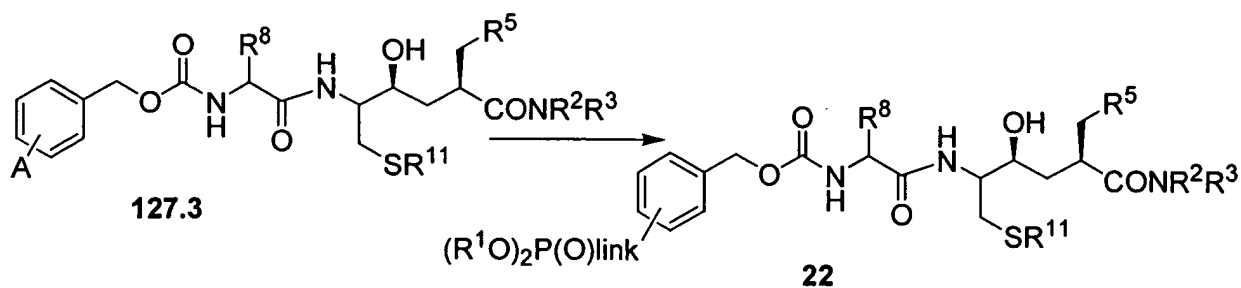
**Scheme 126**



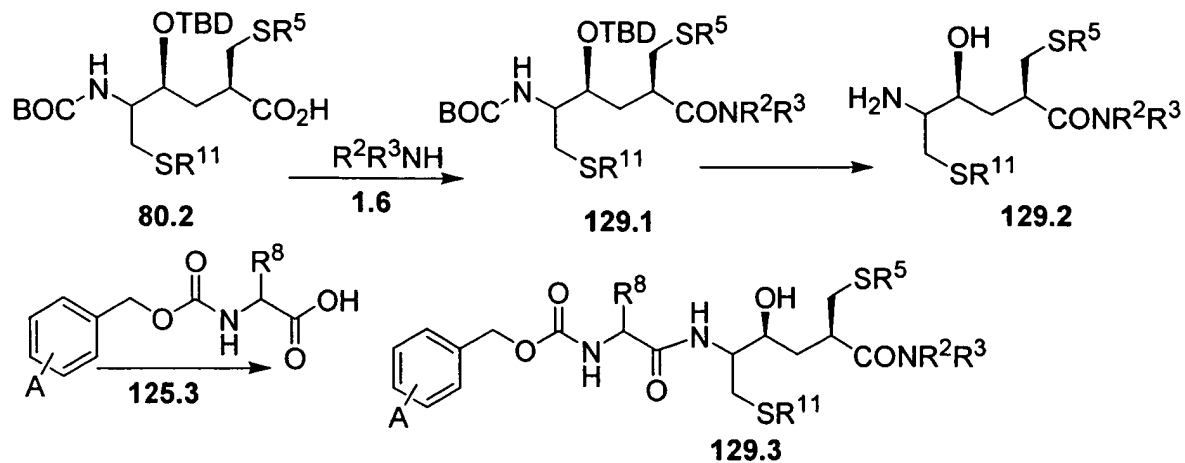
**Scheme 127**



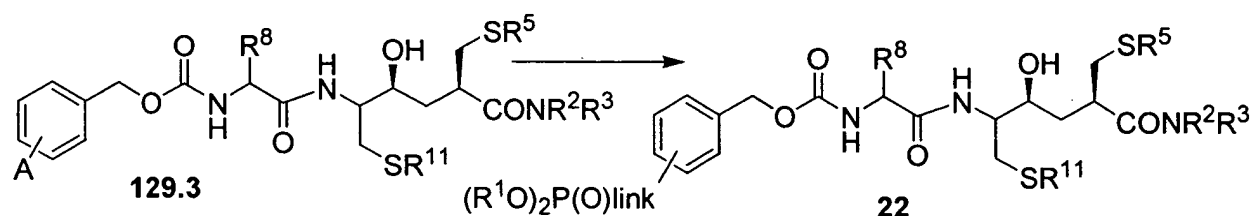
**Scheme 128**



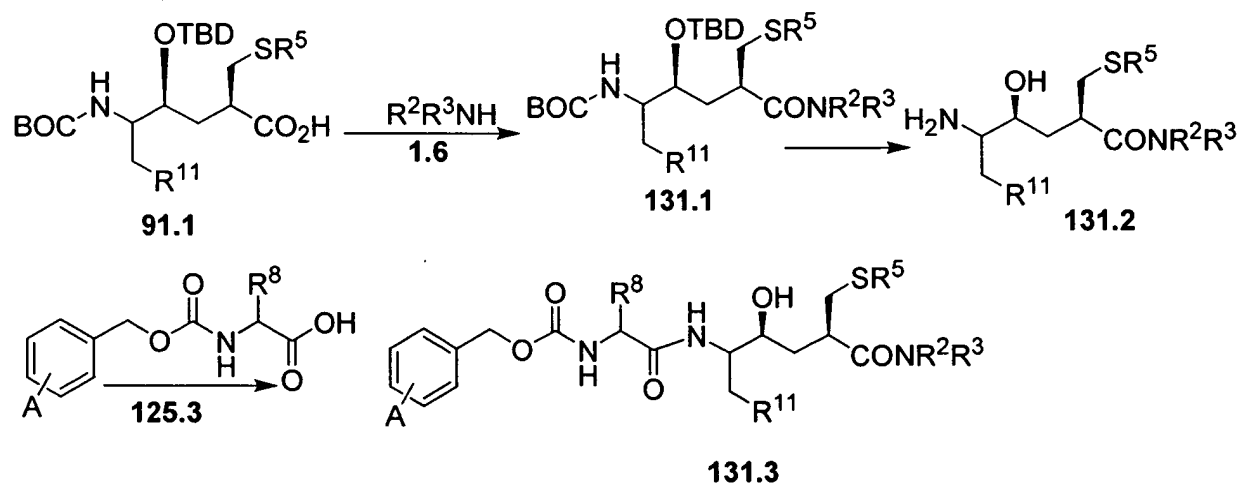
**Scheme 129**



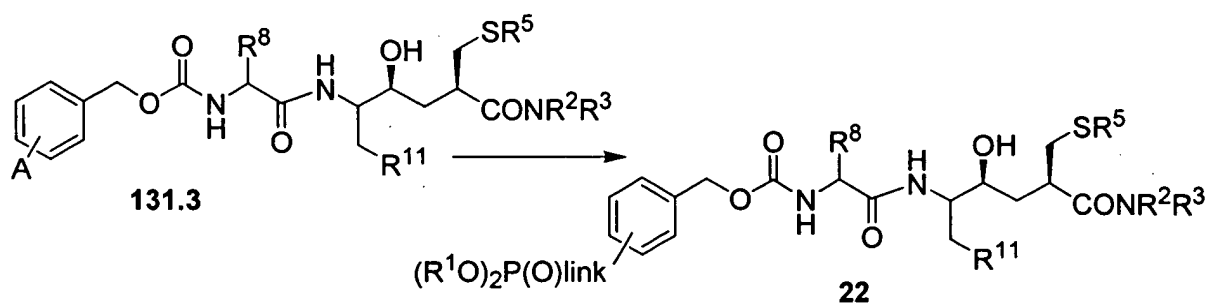
**Scheme 130**



**Scheme 131**



**Scheme 132**



## Preparation of aminoindanol derivatives 1.2 incorporating phosphonate moieties

Scheme 133 illustrates the preparation of variously substituted derivatives of 3-aminoindan-1,2-diol, the preparation of which is described in *J. Med. Chem.*, 1991, 34, 1228. The alcohols, thiols, amines and bromo compounds shown in Scheme 133 can then be transformed into phosphonate-containing reactants 1.2, as described below, (Schemes 134 - 137). The reactants 1.2 are employed in the preparation of the phosphonate esters 1 and 16.

In order to effect changes to the 1-substituent, the starting material 133.1 is transformed into the protected compound 133.2. For example, the aminoalcohol 133.1 is treated with 2-methoxypropene in the presence of an acid catalyst, such as p-toluenesulfonic acid, in a solvent such as tetrahydrofuran, as described in WO9628439, to afford the acetonide-protected product 133.2.

The amino group present in 133.2 is protected to afford the intermediate 133.3, in which R<sup>12</sup> is a protecting group, stable to the subsequent reactions. For example, R<sup>12</sup> can be carbobenzyloxy (cbz), tert-butoxycarbonyl (BOC) and the like, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309.

The free hydroxyl group present in the N-protected acetonide 133.3 is then converted into a suitable leaving group, such as, for example, trifluoromethylsulfonyloxy, p-toluenesulfonyloxy or, preferably, methanesulfonyloxy. This transformation is effected by treatment of 133.3 with a slight molar excess of the corresponding acid chloride or anhydride, in the presence of an organic base.

For example, treatment of 133.3 with methanesulfonyl chloride and pyridine in dichloromethane at ambient temperature affords the mesylate 133.4.

The  $\alpha$ -mesylate group in the product 133.4 is then subjected to displacement reactions with nitrogen, sulfur or oxygen nucleophiles, to effect introduction of the various heteroatoms with inversion of stereochemistry.

For example, the mesylate 133.4 is reacted with a nitrogen nucleophile such as potassium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 399, to afford the amine 133.9.

Preferably, the mesylate 133.4 is reacted, as described in *Angew. Chem. Int. Ed.*, 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such as, for example, dimethylformamide, at ambient temperature, to afford the displacement product

**133.5**, in which  $\text{NR}^a\text{R}^b$  is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in *J. Org. Chem.*, 38, 3034, 1973, then yields the  $\beta$ -amine **133.9**.

The mesylate **133.4** is treated with a sulfur nucleophile, for example potassium thioacetate, as described in *Tetrahedron Lett.*, 1992, 4099, or sodium thiophosphate, as described in *Acta Chem. Scand.*, 1960, 1980, to effect displacement of the mesylate group, followed by mild basic hydrolysis, for example by treatment with aqueous sodium bicarbonate or aqueous ammonia, to afford the  $\beta$ -thiol **133.12**.

Preferably, the mesylate **133.4** is reacted with one molar equivalent of potassium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **133.8**. The product then treated with a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the  $\beta$ -thiol **133.12**.

The mesylate **133.4** is transformed into the  $\beta$ -carbinol **133.7**, by treatment with an oxygen nucleophile. Conversion of sulfonate esters and related compounds to the corresponding carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 481. For example, the mesylate can be reacted with potassium superoxide, in the presence of a crown ether such as 18-crown-6, as described in *Tetrahedron Lett.*, 3183, 1975, to afford the  $\beta$ -carbinol **133.7**.

The carbinol **133.3** is also transformed into the  $\beta$ -bromo compound **133.6**. Methods for the conversion of carbinols to bromo compounds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 356.

For example, the  $\alpha$ -carbinol **133.3** is reacted with hexabromoethane and triphenylphosphine, in an aprotic solvent such as ethyl acetate, as described in *Synthesis*, 139, 1983, to afford the  $\beta$ -bromo compound **133.6**.

Using the above described procedures for the conversion of the  $\alpha$ -carbinol **133.3** into the  $\beta$ -oriented amine **133.9**, thiol **133.12** and bromo compound **133.6**, the  $\beta$ -carbinol **133.7** is transformed into the  $\alpha$ -oriented amine or thiol **133.11** or the bromo compound **133.10**.

Schemes 134 - 137 illustrate the preparation of aminoindanol derivatives incorporating the group  $\text{link-P(O)(OR}^1)_2$ , derived from the intermediates whose syntheses are described above (Scheme 133).

Scheme 134 depicts the preparation of phosphonate esters linked to the aminoindanol nucleus by means of a carbon chain and a heteroatom O, S or N. In this procedure, the hetero-substituted indanol 134.1 is reacted with a bromoalkylphosphonate 134.2, in the presence of a suitable base. The base required for this transformation depends on the nature of the heteroatom X. For example, if X is N or S, an excess of an inorganic base such as, for example, potassium carbonate, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80°C to afford the displacement products 134.3. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide and the like, is employed, in the presence of a solvent such as tetrahydrofuran. Deprotection, by removal of the group R<sup>12</sup>, then affords the amine 134.4.

For example, the β-thiol 133.12 is reacted with an equimolar amount of dialkyl 4-bromobutyl phosphonate 134.5, the preparation of which is described in *Synthesis*, 1999, 9, 909, in dimethylformamide containing excess potassium carbonate, at ca 60°C to afford the thioether phosphonate product 134.6. Deprotection then affords the amine 134.7.

Using the above procedures, but employing, in place of the thiol 133.12, different carbinols, thiols or amines 134.1, and/or different bromoalkylphosphonates 134.2, the corresponding products 134.4 are obtained.

Scheme 135 illustrates the preparation of aminoindanol derivatives in which the phosphonate ester group is attached by means of a nitrogen atom and a carbon chain. In this method, the aminoindanol 135.1 is reacted with a formyl-substituted phosphonate ester, utilizing a reductive amination procedure. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component 135.1 and the aldehyde component 135.2 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 135.3. Deprotection, by removal of the R<sup>12</sup> group, then affords the amine 135.4.

For example, equimolar amounts of the amine 133.11 and a dialkylformylphosphonate 135.5, prepared as described in US 3784590, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in *J. Am. Chem. Soc.*, 91, 3996, 1969, to afford the product 135.6 which is then deprotected to produce the amine 135.7.

Using the above procedures, but employing, in place of the  $\alpha$ -amine **133.11**, the  $\beta$ -amine **133.9**, and/or different formyl-substituted phosphonates **135.2**, the corresponding products **135.4** are obtained.

Scheme **136** depicts the preparation of aminoindanol phosphonates in which the phosphonate moiety is attached to the nucleus by means of a heteroatom and one carbon. In this procedure, a carbinol, thiol or amine **136.1** is reacted with a dialkyl trifluoromethylsulfonyloxy phosphonate **136.2**, in the presence of a suitable base, to afford the alkylation product **136.3**. Deprotection of the product **136.3** then yields the amine **136.4**. The base required for this reaction between **136.1** and **136.2** depends on the nature of the heteroatom X. For example, if X is N or S, an excess of inorganic base such as, for example, potassium carbonate, cesium carbonate or the like, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80° to afford the displacement products **136.3**. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide, sodium hydride or the like, is employed, in the presence of a solvent such as tetrahydrofuran.

For example, the  $\alpha$ -carbinol **133.3** is reacted with one equivalent of lithium hexamethyl disilylazide in tetrahydrofuran, followed by addition of an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate **136.5**, the preparation of which is described in *Tetrahedron Lett.*, 1986, 27, 1497, to afford the ether product **136.6**. Deprotection, by removal of the R<sup>12</sup> group, then affords the amine **136.7**.

Using the above procedures, but employing, in place of the  $\alpha$ -carbinol **133.3**, different carbinols, thiols or amines **136.1**, and /or different dialkyl trifluoromethylsulfonyloxymethyl phosphonates **136.2**, the corresponding products **136.4** are obtained.

Scheme **137** illustrates the preparation of aminoindanol phosphonate esters in which the phosphonate group is attached directly to the aminoindanol nucleus.

In this procedure, the bromoindanol derivative **137.1** is reacted with a sodium dialkyl phosphite, in a suitable aprotic polar solvent such as dimethyl formamide or N-methylpyrrolidinone. Displacement of the bromo substituent occurs to yield the phosphonate **137.3**. Deprotection, by removal of the R<sup>12</sup> group, then affords the amine **137.4**.

For example, equimolar amounts of the  $\alpha$ -bromo compound **133.10** and the dialkyl sodium phosphite **137.2**, are dissolved in dimethylformamide and the mixture is heated at ca.

60°C, as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the  $\beta$ -phosphonate **137.5**. Alternatively, the phosphonate compound **137.5** is obtained by means of an Arbuzov reaction between the bromo compound **133.10** and a trialkyl phosphite  $P(OR^1)_3$ . In this procedure, as described in *Handb. Organophosphorus Chem.*, 1992, 115, the reactants are heated together at ca. 100°C to afford the product **137.5**. Deprotection of the latter compound affords the amine **137.6**.

Using the above procedures, but employing, in place of the  $\alpha$ -bromo compound **133.10**, the  $\beta$ -bromo compound **133.6**, and/or different phosphites **137.2**, the corresponding phosphonates **137.4** are obtained.

### **Preparation of phenylpropionic acid intermediates 5.1 incorporating phosphonate moieties**

Phenylpropionic acid derivatives incorporating the substituent link- $P(O)(OR^1)_2$  are prepared by the reactions illustrated in Schemes **139-143**, using as starting materials variously substituted phenylpropionic acids. The phenylpropionic acid derivatives **5.1** are employed in the preparation of the phosphonate esters **2** in which X is a direct bond.

A number of the substituted phenylpropionic acids required for the reactions shown in Schemes **139-143** are commercially available; in addition, the syntheses of variously substituted phenylpropionic acids have been reported. For those substituted phenylpropionic acids which are not commercially available, and whose syntheses have not been reported, a number of well-established synthetic routes are available. Representative methods for the synthesis of substituted phenylpropionic acids from commercially available starting materials are shown in Scheme **138**.

For example, variously substituted benzaldehydes **138.1** are subjected to a Wittig reaction with carboethoxymethylenetriphenylphosphorane **138.2**, as described in *Ylid Chemistry*, by A. W. Johnson, Academic Press, 1966, p. 132, to afford the corresponding cinnamate esters **138.3**. Equimolar amounts of the reactants **138.1** and **138.2** are heated in an inert solvent such as dioxan or dimethylformamide, at ca 50°C, to afford the product **138.3**. Reduction of the double bond in the product **138.3** then afford the saturated ester **138.6**, (X = H) which upon hydrolysis yields the phenylpropionic acid intermediate **138.10**.

Methods for the reduction of carbon-carbon double bonds are described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, p. 6. Typical of the available reduction methods are catalytic hydrogenation, for example using palladium catalysts, as

described in Hydrogenation Methods, by P. N. Rylander, Academic Press, New York, 1985, hydroboration-protonolysis, as described in *J. Am. Chem. Soc.*, 81, 4108, 1959, or diimide reduction, as described in *J. Org. Chem.*, 52, 4665, 1987. The choice of a particular reduction method is made by one skilled in the art, depending on the nature of the substituent groups attached to the cinnamic acid ester **138.3**.

Alternatively, the cinnamic esters **138.3** are obtained by means of a palladium-catalyzed Heck reaction between an appropriately substituted bromobenzene **138.5** and ethyl acrylate **138.4**. In this procedure, a substituted bromobenzene **138.5** is reacted with ethyl acrylate in the presence of a palladium (II) catalyst, as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the cinnamate ester **138.3**. Equimolar amounts of the reactants **138.4** and **138.5** are dissolved in a polar aprotic solvent such as dimethylformamide or tetrahydrofuran, at a temperature of about 60°C, in the presence or ca. 3 mol % of, for example, bis(triphenylphosphine)palladium (II) chloride and triethylamine, to afford the product **138.3**.

Alternatively, the substituted phenylpropionic acid intermediates are obtained from the correspondingly substituted methylbenzenes **138.7**. In this procedure, the methylbenzene **138.7** is subjected to free-radical bromination, for example by reaction with an equimolar amount of N-bromosuccinimide, as described in *Chem. Rev.*, 63, 21, 1963, to afford the bromomethyl derivative **138.8**. The latter compound is then reacted with a salt of an ester of malonic acid, for example the sodium salt of diethyl malonate **138.9**, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 489, to afford the displacement product **138.6**, (X = COOEt). The latter compound is subjected to hydrolysis and decarboxylation, for example by treatment with aqueous alkali or dilute aqueous acid, to afford the phenylpropionic acid **138.10**.

Scheme **139** illustrates the preparation of phosphonate-containing phenylpropionic acids in which the phosphonate moiety is attached to the phenyl ring by means of an aromatic group.

In this procedure, the carboxyl group of a bromo-substituted phenylpropionic acid **139.1** is protected. Methods for the protection of carboxylic acids are described, for example, in

Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224. The product **139.2** is then subjected to halogen-methyl exchange, for example by reaction with an alkyllithium, to afford the product **139.3** in which M is Li. The latter compound is subjected to palladium (II) or palladium (0) catalyzed coupling, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. Compound

**139.3** is first converted into the boronic acid **139.4**, by reaction with a trialkyl borate, and the boronic acid product is coupled with a dialkyl bromophenylphosphonate **139.5** to yield the product **139.6**. Deprotection then affords the intermediate phosphonate-substituted phenylpropionic acid **139.7**.

For example, 4-bromophenylpropionic acid **139.8**, prepared as described in U.S. 4,032,533, is converted into the acid chloride, by treatment with thionyl chloride, oxalyl chloride and the like. The acid chloride is then reacted with 3-methyl-3-oxetanemethanol **139.9** (Aldrich), in the presence of a tertiary organic base such as pyridine, in a solvent such as dichloromethane, to afford the ester **139.10**. This product is then rearranged by treatment with boron trifluoride etherate in dichloromethane, at about -15°C as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 268, to yield the orthoester **139.11**, known as an OBO ester. The latter product is then reacted with one molar equivalent of n-butyllithium, in a solvent such as ether, at about -80°C, to afford the lithio derivative, which is reacted with a trialkyl borate, as described in J. Organomet. Chem., 1999, 581, 82, to yield the boronate **139.12**. This material is coupled, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0), and an inorganic base such as sodium carbonate, with a dialkyl 4-bromophenylphosphonate **139.13**, prepared as described in *J. Chem. Soc., Perkin Trans.*, 1977, 2, 789, to give the coupled product **139.14**. Deprotection, for example by treatment with aqueous pyridine p-toluenesulfonate, as described in *Can. J. Chem.*, 61, 712, 1983, then affords the carboxylic acid **139.15**.

Using the above procedures, but employing, in place of the 4-bromophenylpropionic acid **139.8**, different bromophenylpropionic acids **139.1**, and/or different dialkyl bromophenyl phosphonates **139.5**, the corresponding products **139.7** are obtained.

Scheme 140 depicts the preparation of phenylpropionic acids in which a phosphonate ester is attached to the phenyl ring by means of a heteroatom. In this procedure, a suitably protected hydroxy, thio or amino-substituted phenyl propionic acid **140.1** is reacted with a derivative of a hydroxymethyl dialkylphosphonate **140.2**, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product **140.3**. Deprotection then affords the carboxylic acid **140.4**.

For example, trichloroethyl 3-hydroxyphenylpropionic acid **140.5**, prepared by reaction of 3-hydroxyphenylpropionic acid (Fluka) with trichloroethanol and dicyclohexylcarbodiimide, as described in *J. Am. Chem. Soc.*, 88, 852, 1966, is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **140.6**, prepared as described in *Tetrahedron Lett.*, 1986, 27, 1477, to afford the ether product **140.7**. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C, to afford the product **140.7**. Removal of the trichloroethyl ester group, for example by treatment with zinc in acetic acid at 0°C, as described in *J. Am. Chem. Soc.*, 88, 852, 1966, then yields the carboxylic acid **140.8**.

Using the above procedures, but employing, in place of the phenol **140.5**, different phenols, thiols or amines **140.1**, and/or different phosphonates **140.2**, the corresponding products **140.4** are obtained.

Scheme **141** illustrates the preparation of phenylpropionic acids in which a phosphonate moiety is attached by means of a chain incorporating a heteroatom. In this procedure, a carboxyl protected halomethyl substituted phenylpropionic acid **141.1** is reacted with a dialkyl hydroxy, thio or amino-substituted alkylphosphonate **141.2**. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **141.2**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed.

For example, 4-bromomethyl phenylpropionic acid, prepared as described in U.S. 4,032,533, is converted into the methoxymethyl ester **141.5**, by reaction with methoxymethyl chloride and triethylamine in dimethylformamide, as described in *J. Chem. Soc.*, 2127, 1965. Equimolar amounts of the ester **141.5** and a dialkyl 2-aminoethyl phosphonate **141.6**, prepared as described in *J. Org. Chem.*, 2000, 65, 676, are reacted in dimethylformamide at ca 80°C, in the presence of potassium carbonate, to afford the displacement product **141.7**. Deprotection, for example by treatment with trimethylsilyl bromide and a trace of methanol, as described in *Aldrichimica Acta*, 11, 23, 1978, then yields the carboxylic acid **141.8**.

Using the above procedures, but employing, in place of the amine **141.6**, different amines, alcohols or thiols **141.2** and/or different halomethyl-substituted phenylpropionic acids **141.1**, the corresponding products **141.4** are obtained.

Scheme 142 illustrates the preparation of phosphonate esters attached to the phenyl ring by means of an oxygen or sulfur link, by means of a Mitsunobu reaction. In this procedure, a protected hydroxy- or thio-substituted phenylpropionic acid **142.1** is reacted with a dialkyl hydroxyalkyl phosphonate **142.2**. The condensation reaction between **142.1** and **142.2** is effected in the presence of a triaryl phosphine and diethyl azodicarboxylate, as described in *Org. React.*, 1992, 42, 335. The product **142.3** is then deprotected to afford the carboxylic acid **142.4**.

For example, 3-mercaptophenylpropionic acid (Apin Chemicals) is converted into the tert. butyl ester **142.5**, by treatment with carbonyl diimidazole, tert. butanol and diazabicycloundecene, as described in *Synthesis*, 833, 1982. The ester is reacted with a dialkyl hydroxymethylphosphonate **142.6**, prepared as described in *Synthesis*, 4, 327, 1998, in the presence of triphenyl phosphine, triethylamine and diethyl azodicarboxylate, to afford the thioether **142.7**. The tert. butyl group is removed by treatment with formic acid at ambient temperature, as described in *J. Org. Chem.*, 42, 3972, 1977, to yield the carboxylic acid **142.8**.

Using the above procedures, but employing, in place of the thiol **142.5**, different phenols or thiols **142.1** and/or different hydroxyalkyl phosphonates **142.2**, the corresponding products **142.4** are obtained.

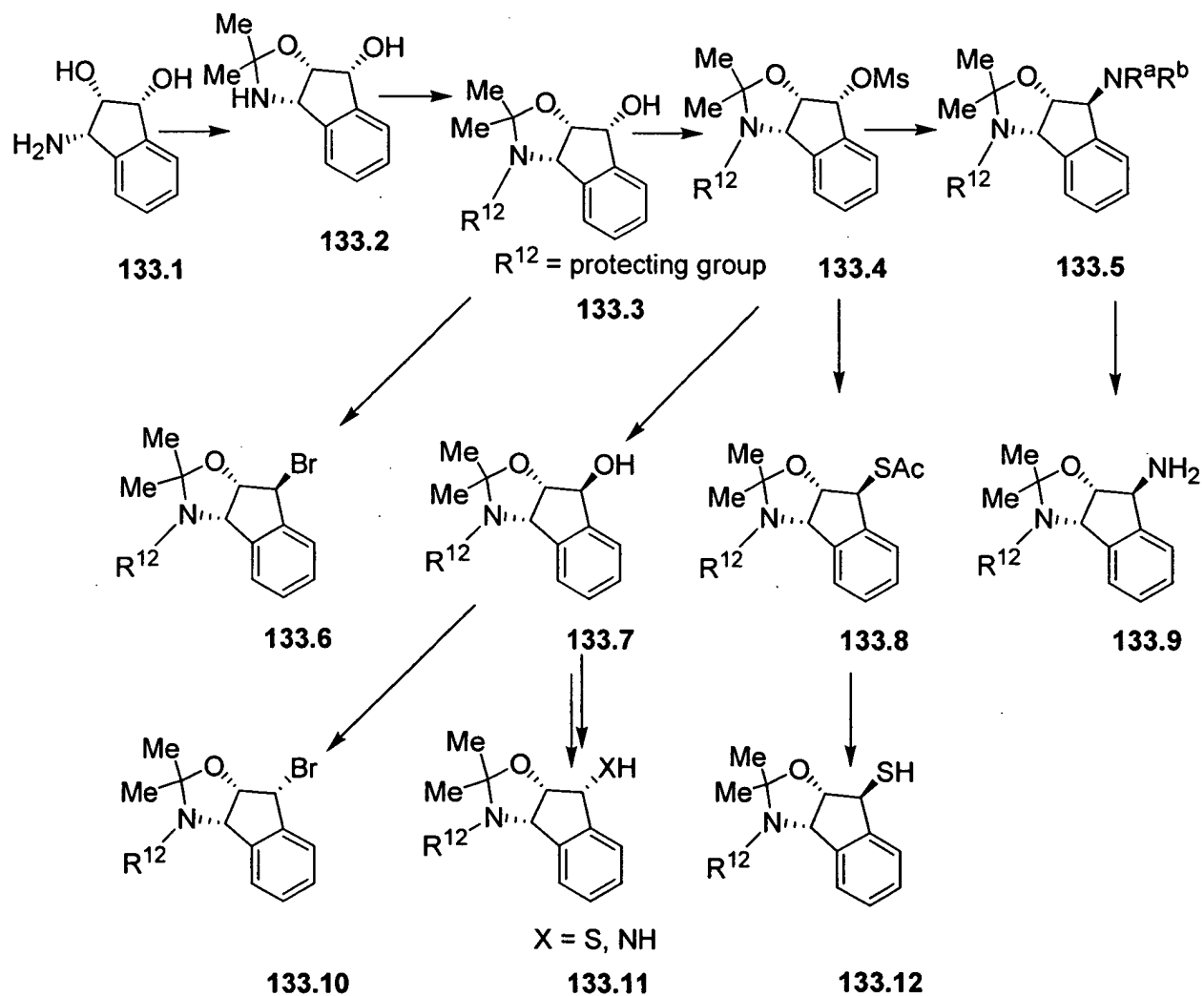
Scheme 143 depicts the preparation of phenylpropionic acids linked to a phosphonate ester by means of an aromatic or heteroaromatic ring. The products **143.3** are obtained by means of an alkylation reaction in which a bromomethyl aryl or heteroaryl phosphonate **143.1** is reacted with a carboxyl-protected hydroxy, thio or amino-substituted phenylpropionic acid **140.1**. The reaction is conducted in the presence of a base, the nature of which is determined by the substituent X in the reactant **140.1**. For example, if X is O, a strong base such as lithium hexamethyldisilylazide or sodium hydride is employed. If X is S or N, an organic or inorganic base, such as diisopropylethylamine or cesium carbonate is employed. The alkylated product **143.2** is then deprotected to afford the carboxylic acid **143.3**.

For example, 3-(4-aminophenyl)propionic acid (Aldrich) is reacted with tert. butyl chlorodimethylsilane and imidazole in dimethylformamide, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 262, to afford the silyl ester **143.4**. This compound is reacted with an equimolar amount of a dialkyl 4-bromomethylbenzylphosphonate **143.5**, prepared as described in *Tetrahedron Lett.*, 1998, 54, 9341, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to

afford the product **143.6**. The silyl ester is removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972, to give the carboxylic acid **143.7**.

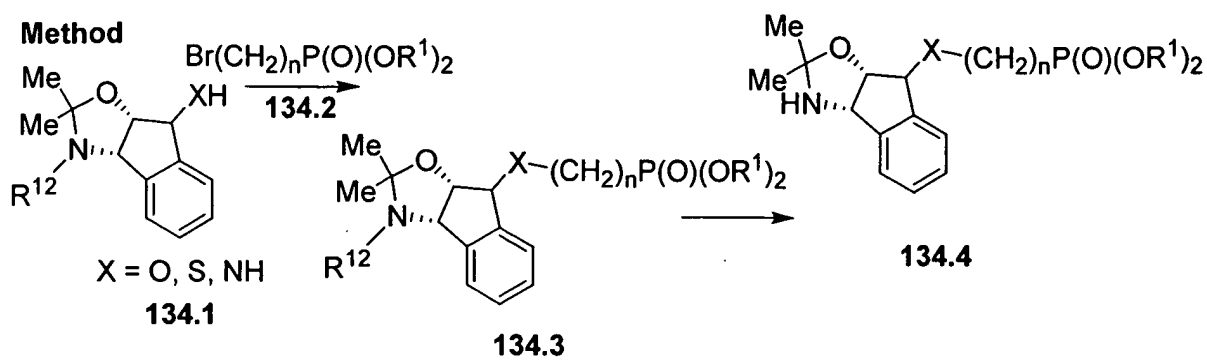
Using the above procedures, but employing, in place of the amino compound **143.4**, different phenols, mercaptans or amines **140.1**, and/or different halomethyl phosphonates **143.1**, the corresponding products **143.3** are obtained.

**Scheme 133**

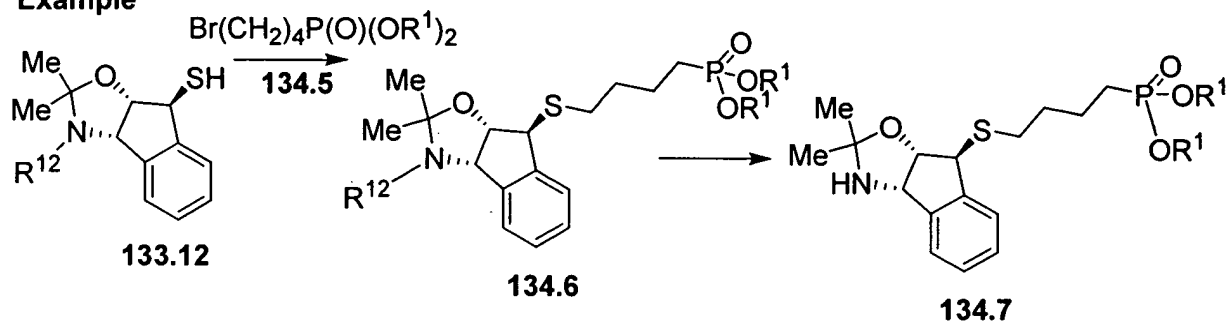


### Scheme 134

#### Method

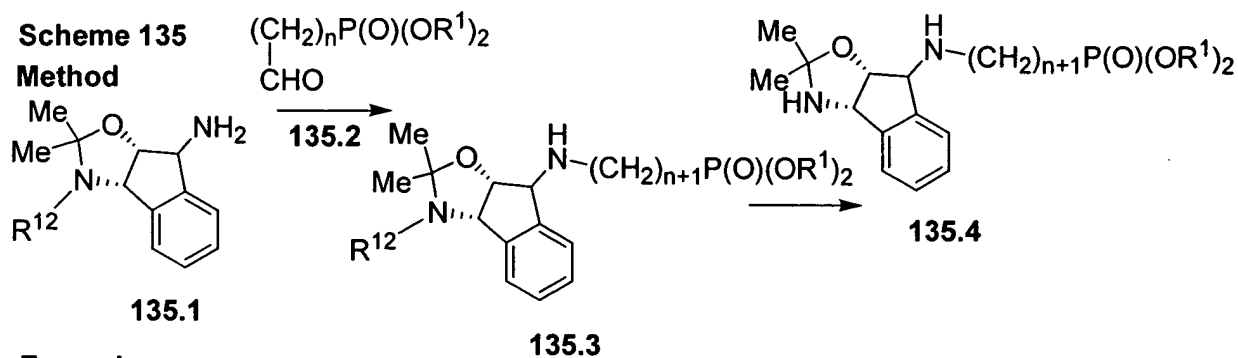


#### Example

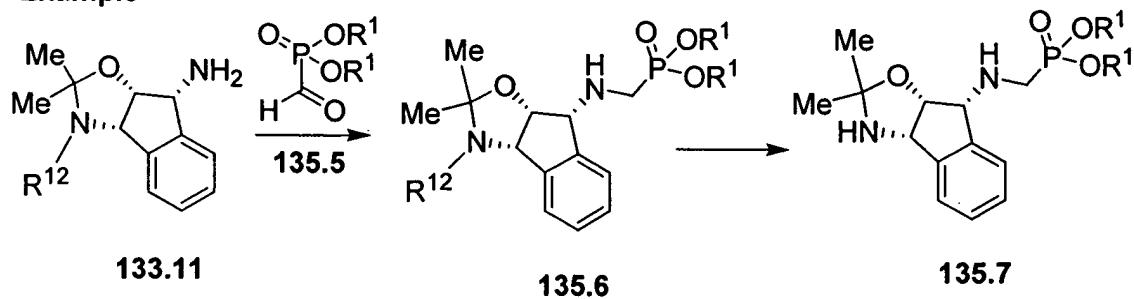


### Scheme 135

#### Method

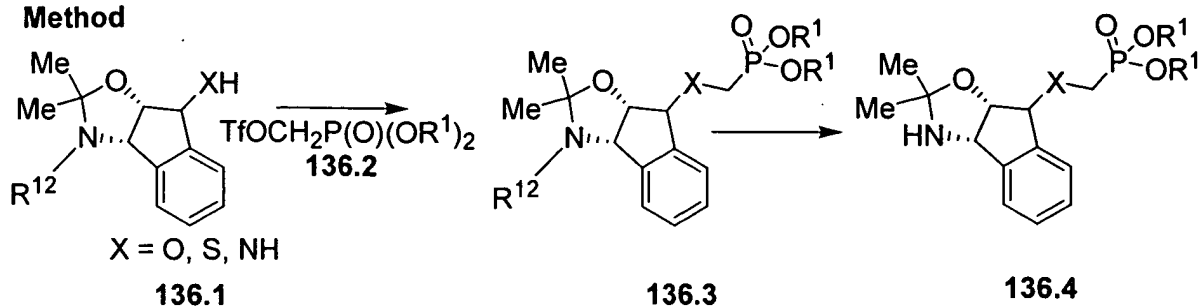


#### Example

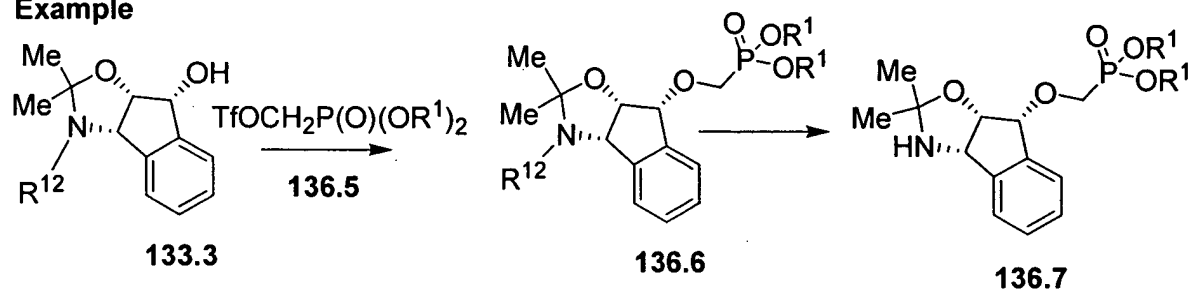


### Scheme 136

#### Method

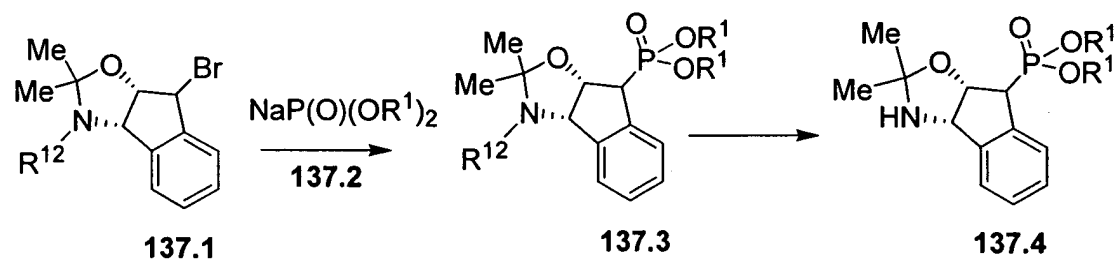


#### Example

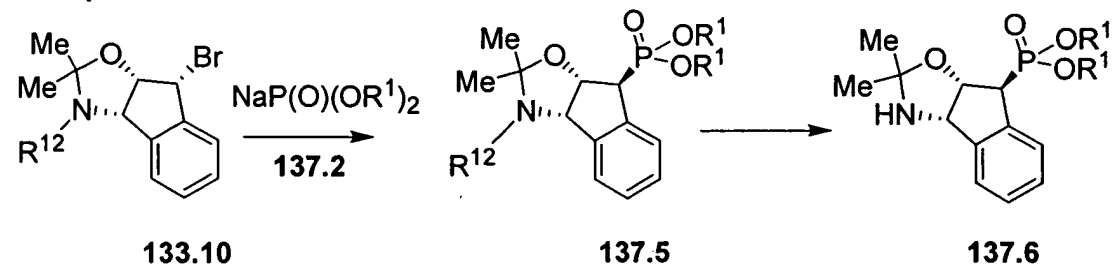


### Scheme 137

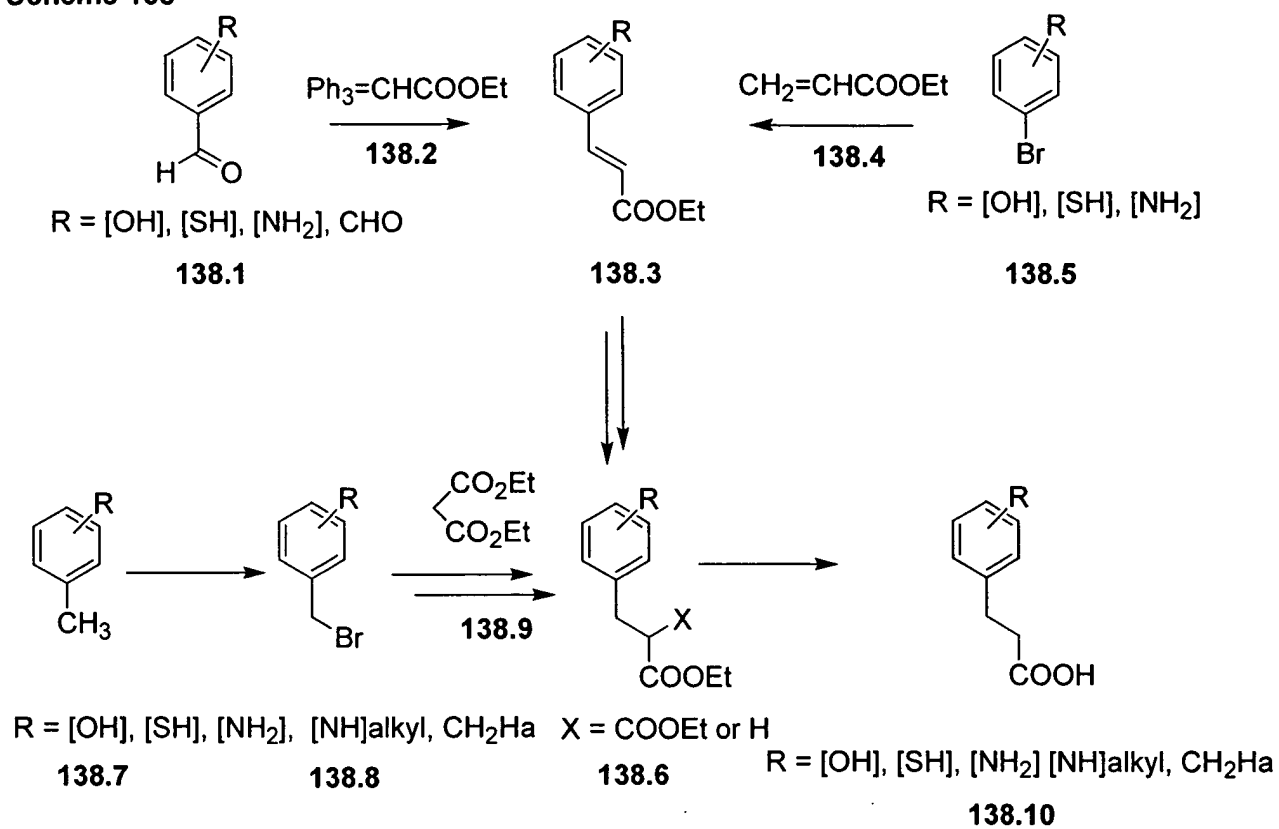
#### Method



#### Example

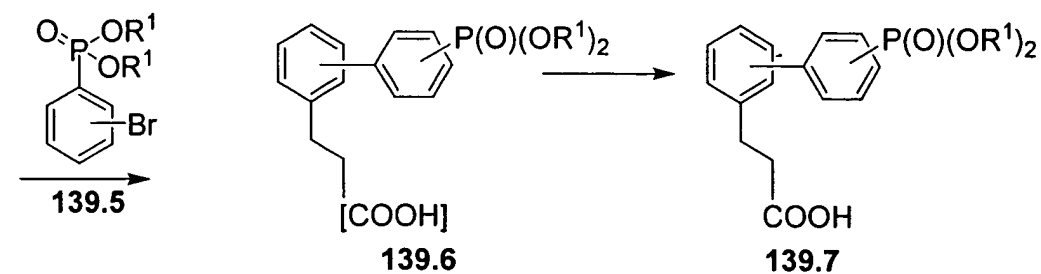
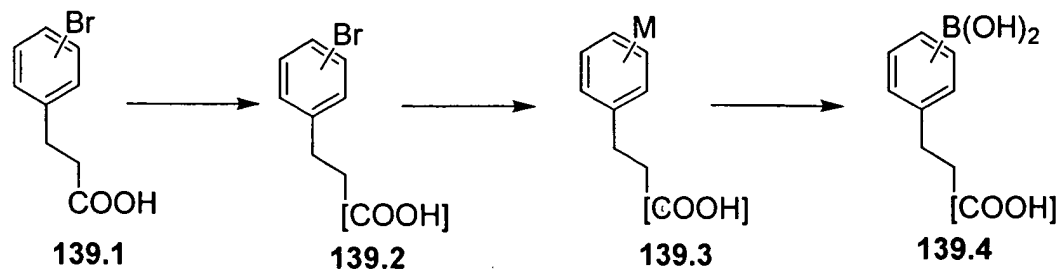


**Scheme 138**

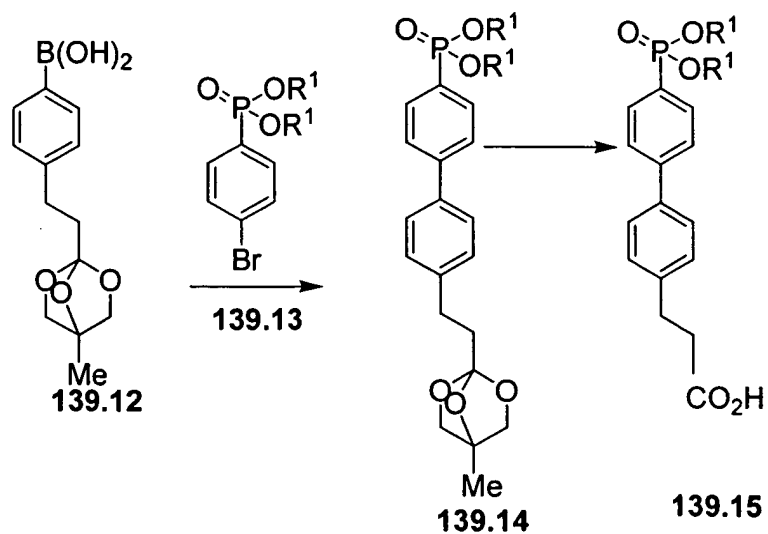
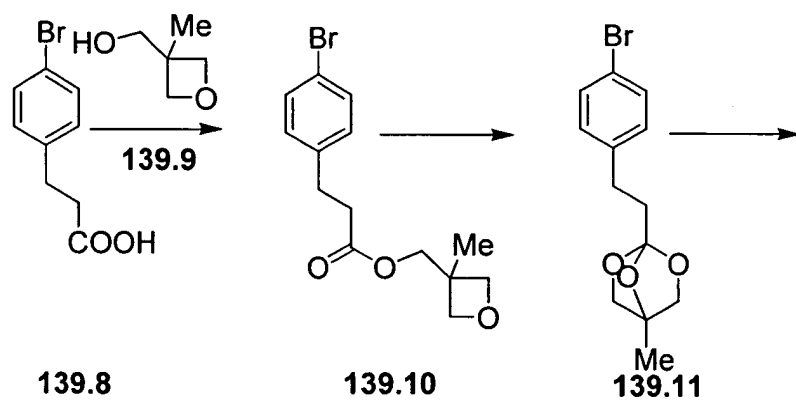


# Scheme 139

## Method



## Example



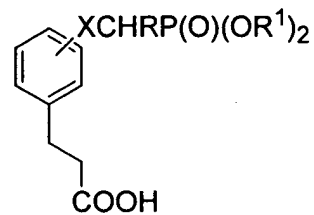
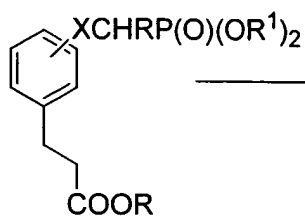
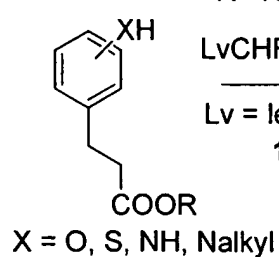
### Scheme 140

#### Method

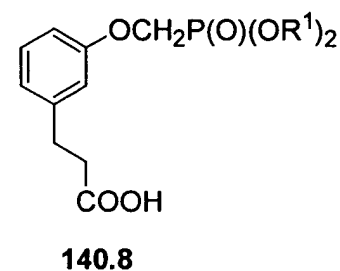
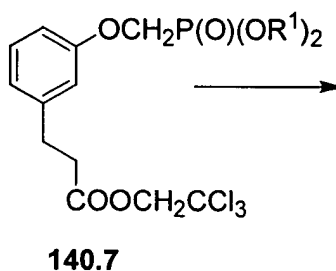
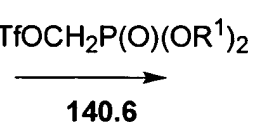
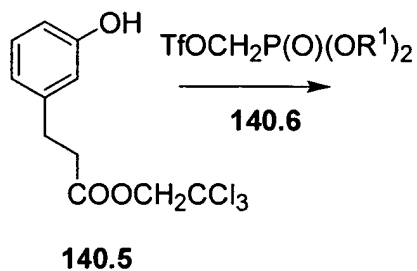
R = H or alkyl



Lv = leaving group  
**140.2**

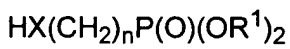


#### Example

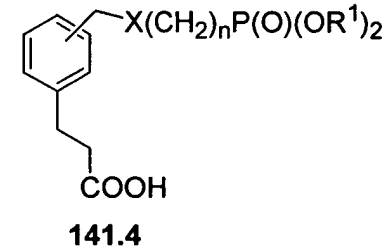
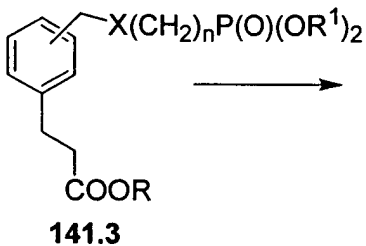
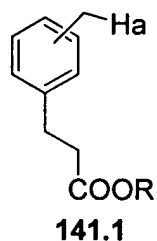


### Scheme 141

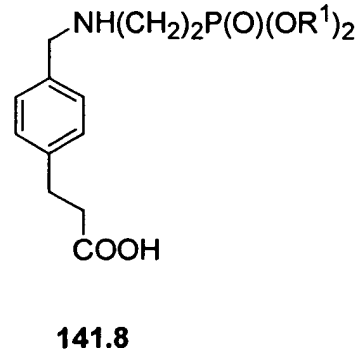
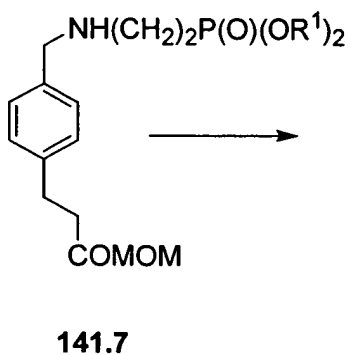
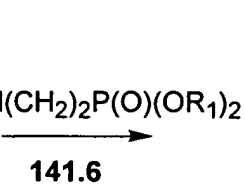
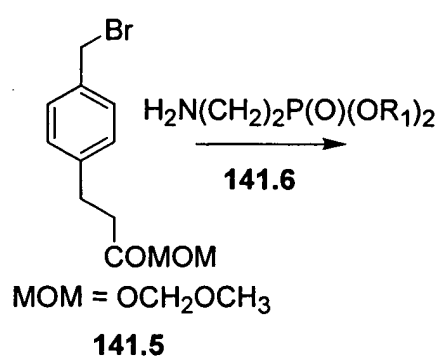
#### Method



X = O, S, NH, Nalkyl  
**141.2**

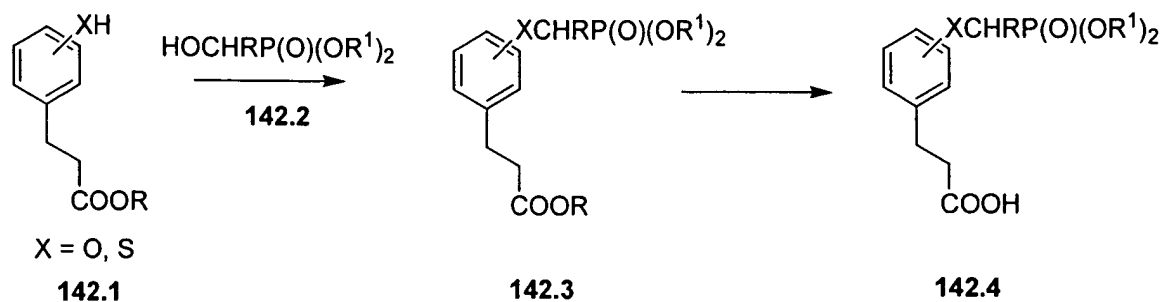


#### Example

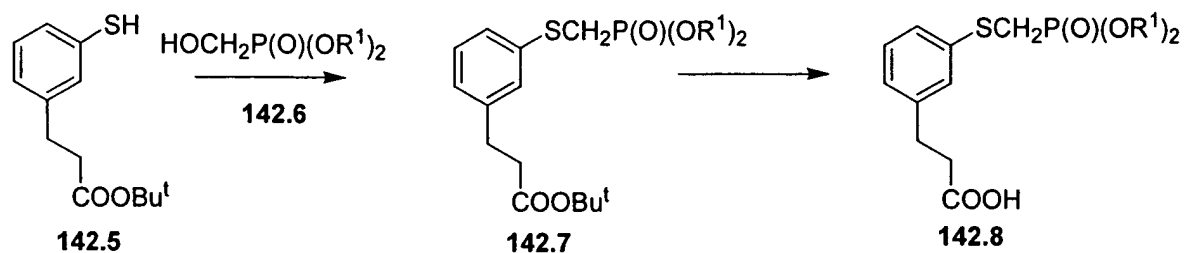


# Scheme 142

## Method

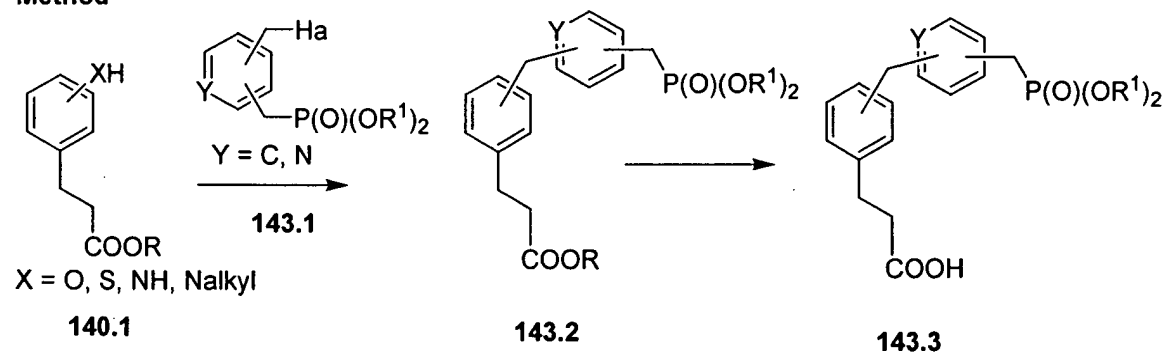


## Example

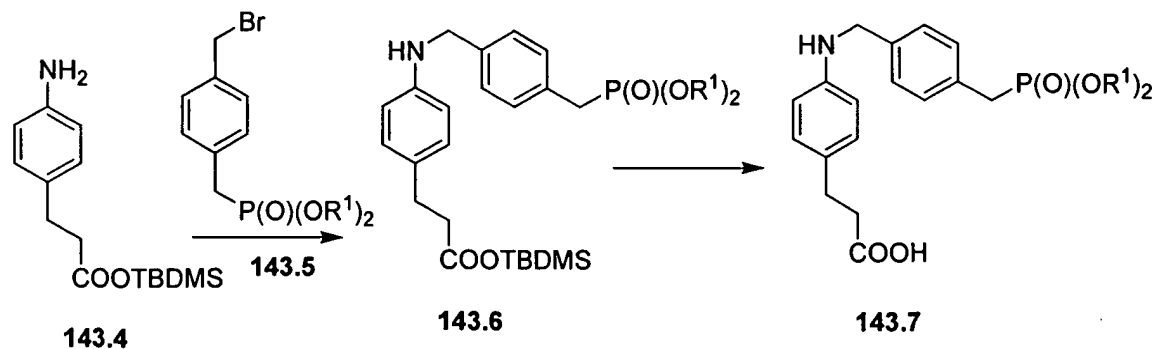


# Scheme 143

## Method



## Example



## Preparation of the phosphonate-containing thiophenol derivatives 7.1

Schemes 144 - 153 describe the preparation of phosphonate-containing thiophenol derivatives 7.1 which are employed in the preparation of the phosphonate ester intermediates 2, 14 and 19 in which X is sulfur, and of the intermediate 15 in which X' is sulfur.

Scheme 144 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 144.1 is protected to afford the product 144.2. The protection and deprotection of thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in *Bull. Chem. Soc. Jpn.*, 37, 433, 1974. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 144.3, to afford the phosphonate ester 144.4. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. The thiol protecting group is then removed, as described above, to afford the thiol 144.5.

For example, 3-bromothiophenol 144.6 is converted into the 9-fluorenylmethyl (Fm) derivative 144.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in *Int. J. Pept. Protein Res.*, 20, 434, 1982. The product is then reacted with a dialkyl phosphite 144.3 to afford the phosphonate ester 144.8. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. The compound 144.7 is reacted, in toluene solution at reflux, with a dialkyl phosphite 144.3, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the phosphonate product 144.8. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in *J. Chem. Soc., Chem. Comm.*, 1501, 1986, to give the thiol 144.9.

Using the above procedures, but employing, in place of 3-bromothiophenol **144.6**, different thiophenols **144.1**, and/or different dialkyl phosphites **144.3**, the corresponding products **144.5** are obtained.

Scheme **145** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **145.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkylolithium reagent, to afford the metallated derivative **145.3**. The latter compound is reacted with a halodialkyl phosphite **145.4** to afford the product **145.5**; deprotection then affords the thiophenol **145.6**.

For example, 4-bromothiophenol **145.7** is converted into the S-triphenylmethyl (trityl) derivative **145.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 287. The product is converted into the lithium derivative **145.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite **145.10** to afford the phosphonate **145.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in *J. Org. Chem.*, 31, 1118, 1966, then affords the thiol **145.12**.

Using the above procedures, but employing, in place of the bromo compound **145.7**, different halo compounds **145.1**, and/or different halo dialkyl phosphites **145.4**, there are obtained the corresponding thiols **145.6**.

Scheme **146** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol **146.1** is subjected to free-radical bromination to afford a bromomethyl product **146.2**. This compound is reacted with a sodium dialkyl phosphite **146.3** or a trialkyl phosphite, to give the displacement or rearrangement product **146.4**, which upon deprotection affords the thiophenol **146.5**.

For example, 2-methylthiophenol **146.5** is protected by conversion to the benzoyl derivative **146.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **146.8**. This material is reacted with a sodium dialkyl phosphite **146.3**, as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the product **146.9**. Alternatively, the bromomethyl compound **146.8** is converted into the phosphonate **146.9** by

means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **146.8** is heated with a trialkyl phosphate  $P(OR^1)_3$  at ca.  $100^\circ C$  to produce the phosphonate **146.9**. Deprotection of the phosphonate **146.9**, for example by treatment with aqueous ammonia, as described in *J. Am. Chem. Soc.*, 85, 1337, 1963, then affords the thiol **146.10**.

Using the above procedures, but employing, in place of the bromomethyl compound **146.8**, different bromomethyl compounds **146.2**, there are obtained the corresponding thiols **146.5**.

Scheme **147** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **147.1** is reacted with a dialkyl hydroxyalkylphosphonate **147.2** under the conditions of the Mitsunobu reaction, for example as described in *Org. React.*, 1992, 42, 335, to afford the coupled product **147.3**. Deprotection then yields the O- or S-linked products **147.4**.

For example, 3-hydroxythiophenol, **147.5**, is converted into the monotrityl ether **147.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **147.7** in benzene, as described in *Synthesis*, 4, 327, 1998, to afford the ether compound **147.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **147.9**.

Using the above procedures, but employing, in place of the phenol **147.5**, different phenols or thiophenols **147.1**, there are obtained the corresponding thiols **147.4**.

Scheme **148** illustrates the preparation of thiophenols **148.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **148.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **148.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **148.3**. Deprotection then affords the thiol **148.4**.

For example, 4-methylaminothiophenol **148.5** is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298, to afford the S-acetyl product **148.6**. This material is then reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **148.7**, the preparation of which is described in *Tetrahedron Lett.*, 1986, 27, 1477, to afford the displacement product **148.8**. Preferably,

equimolar amounts of the phosphonate **148.7** and the amine **148.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **148.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in *J. Am. Chem. Soc.*, 85, 1337, 1963, then affords the thiophenol **148.9**.

Using the above procedures, but employing, in place of the thioamine **148.5**, different phenols, thiophenols or amines **148.1**, and/or different phosphonates **148.2**, there are obtained the corresponding products **148.4**.

Scheme **149** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **149.2**. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol **149.1** is reacted with a dialkyl bromoalkyl phosphonate **149.2** to afford the product **149.3**. Deprotection then affords the free thiophenol **149.4**.

For example, 3-hydroxythiophenol **149.5** is converted into the S-trityl compound **149.6**, as described above. This compound is then reacted with a dialkyl 4-bromobutyl phosphonate **149.7**, the synthesis of which is described in *Synthesis*, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product **149.8**. Deprotection, as described above, then affords the thiol **149.9**.

Using the above procedures, but employing, in place of the phenol **149.5**, different phenols, thiophenols or amines **149.1**, and/or different phosphonates **149.2**, there are obtained the corresponding products **149.4**.

Scheme **150** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **150.2** is coupled with an aromatic bromo compound **150.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan,

in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **150.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **150.4**, or the saturated analog **150.6**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **150.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **150.8**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **150.9**. Deprotection, as described above, then affords the thiol **150.10**. Optionally, the initially formed unsaturated phosphonate **150.9** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme 138, to yield the saturated product **150.11**, which upon deprotection affords the thiol **150.12**.

Using the above procedures, but employing, in place of the bromo compound **150.7**, different bromo compounds **150.1**, and/or different phosphonates **150.2**, there are obtained the corresponding products **150.4** and **150.6**.

Scheme 151 illustrates the preparation of an aryl-linked phosphonate ester **151.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **151.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in *J. Org. Chem.*, 49, 5237, 1984. A coupling reaction then affords the diaryl product **151.3** which is deprotected to yield the thiol **151.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in *J. Organomet. Chem.*, 1999, 581, 82, affords the boronate **151.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **151.6**, the preparation of which is described in *J. Chem. Soc.*, Perkin

Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **151.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **151.8**.

Using the above procedures, but employing, in place of the boronate **151.5**, different boronates **151.1**, and/or different phosphonates **151.2**, there are obtained the corresponding products **151.4**.

Scheme **152** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **152.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **152.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **152.3** is then deprotected to afford the thiol **152.4**.

For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **152.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **152.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **152.6**, the preparation of which is described in *Tetrahedron*, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product **152.7** thus obtained is deprotected, as described above, to afford the thiol **152.8**.

Using the above procedures, but employing, in place of the thiophenol **152.5**, different phenols, thiophenols or amines **152.1**, and/or different phosphonates **152.2**, there are obtained the corresponding products **152.4**.

Scheme **153** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol **153.1**, for example an indoline (in which X-Y is (CH<sub>2</sub>)<sub>2</sub>), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is (CH<sub>2</sub>)<sub>3</sub>) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **153.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **153.3**. Deprotection, as described above, then affords the thiol

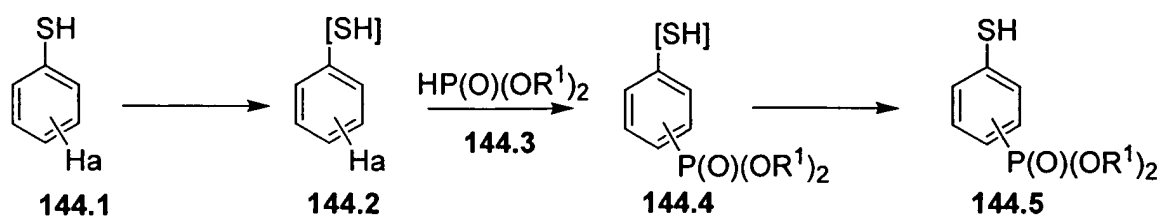
**153.4.** The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in *J. Org. Chem.*, 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in *Synthesis*, 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in *Tetrahedron Lett.*, 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in *J. Het. Chem.*, 1991, 28, 1517, and in *J. Med. Chem.*, 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in *Sulfur Letters*, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky *et al.*, eds, Pergamon, 1995, Vol. 2, p. 707.

For example, 2,3-dihydro-1H-indole-5-thiol, **153.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **153.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **153.7**, using the conditions described above for the preparation of the phosphonate **148.8**, (Scheme **148**), to yield the phosphonate **153.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **153.9**.

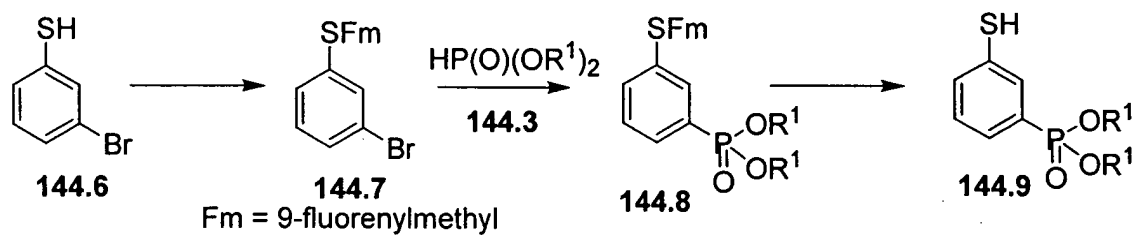
Using the above procedures, but employing, in place of the thiol **153.5**, different thiols **153.1**, and/or different triflates **153.2**, there are obtained the corresponding products **153.4**.

# Scheme 144

## Method

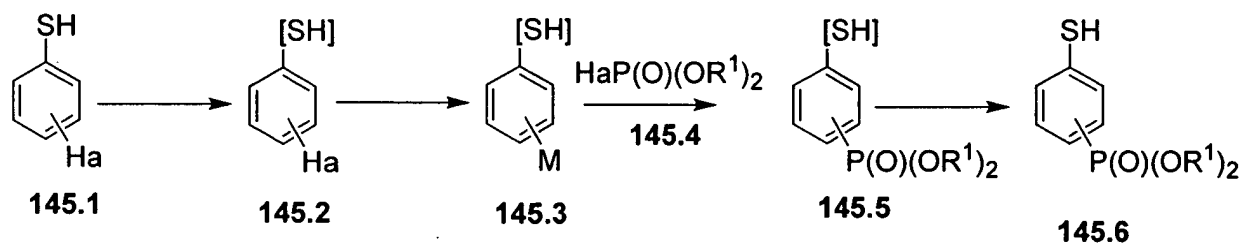


## Example

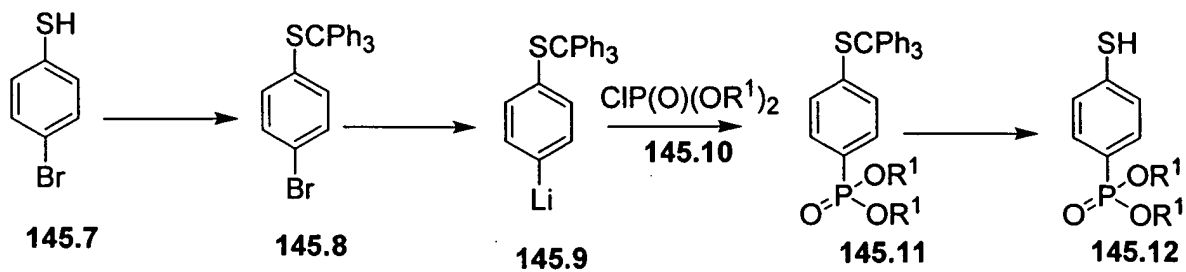


# Scheme 145

## Method

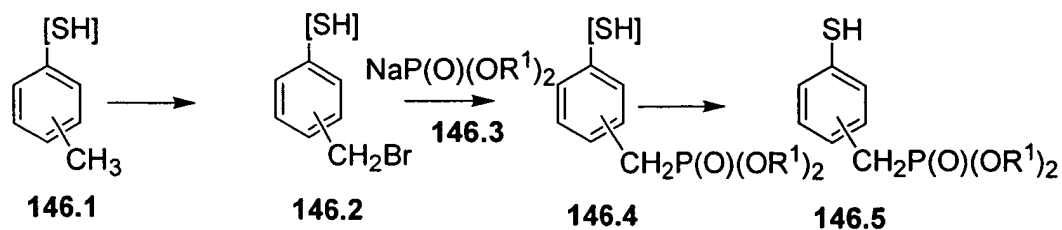


## Example

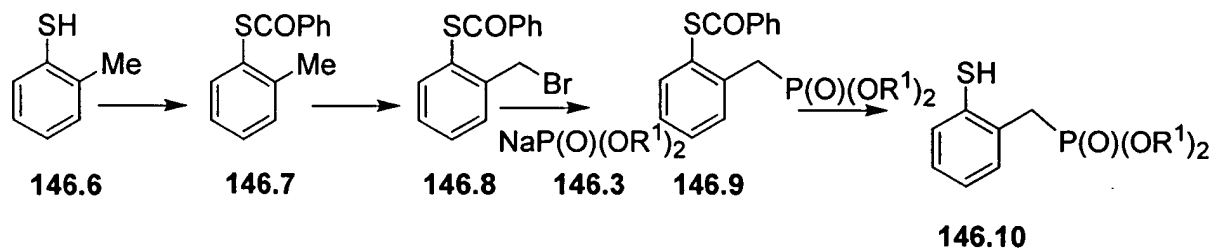


# Scheme 146

## Method

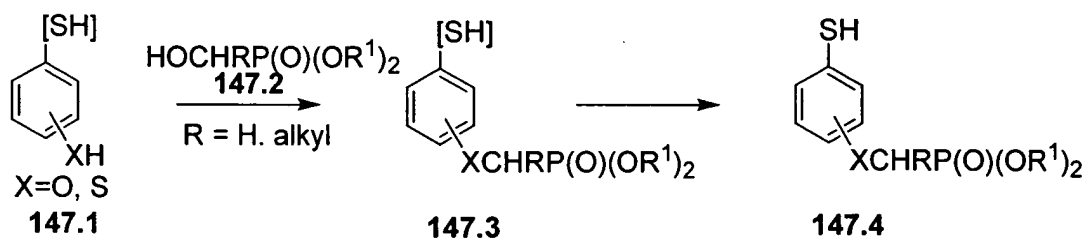


## Example

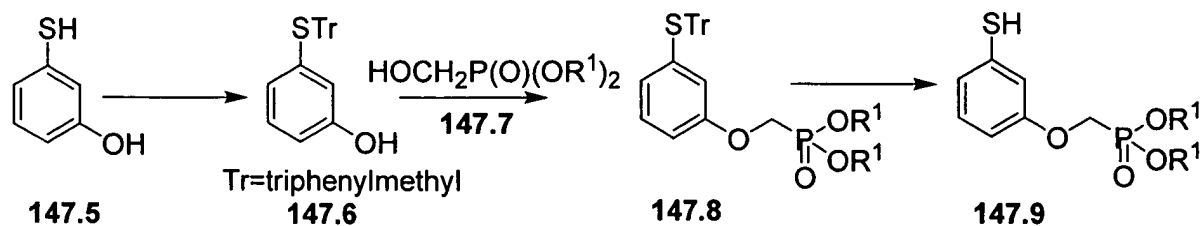


# Scheme 147

## Method

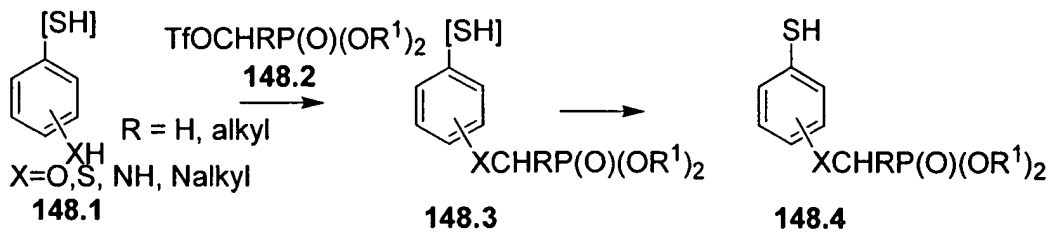


## Example

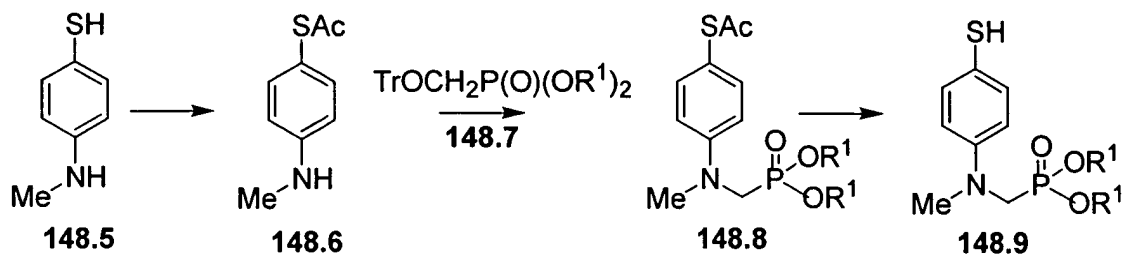


# Scheme 148

## Method

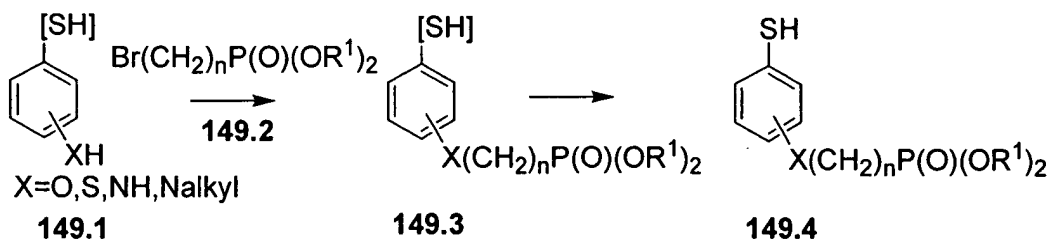


## Example

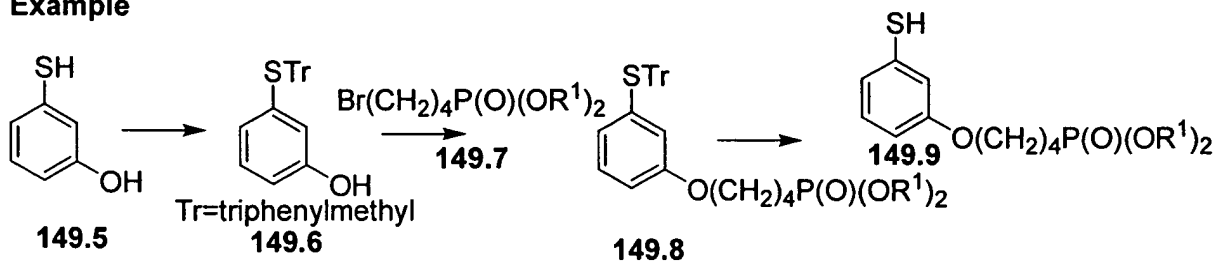


# Scheme 149

## Method

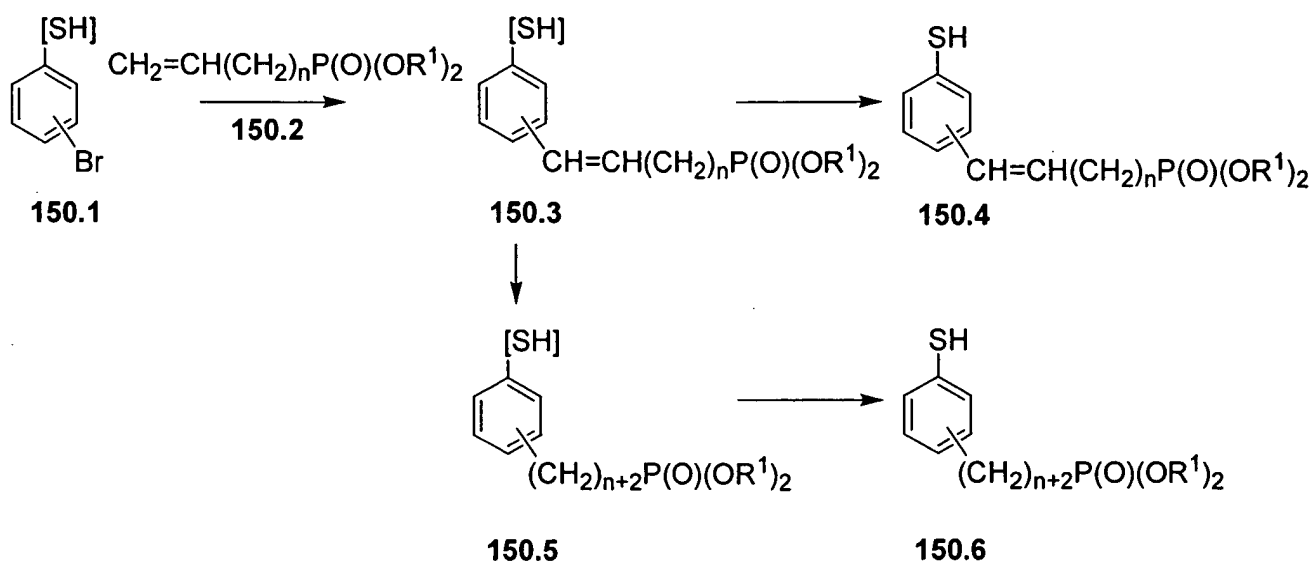


## Example

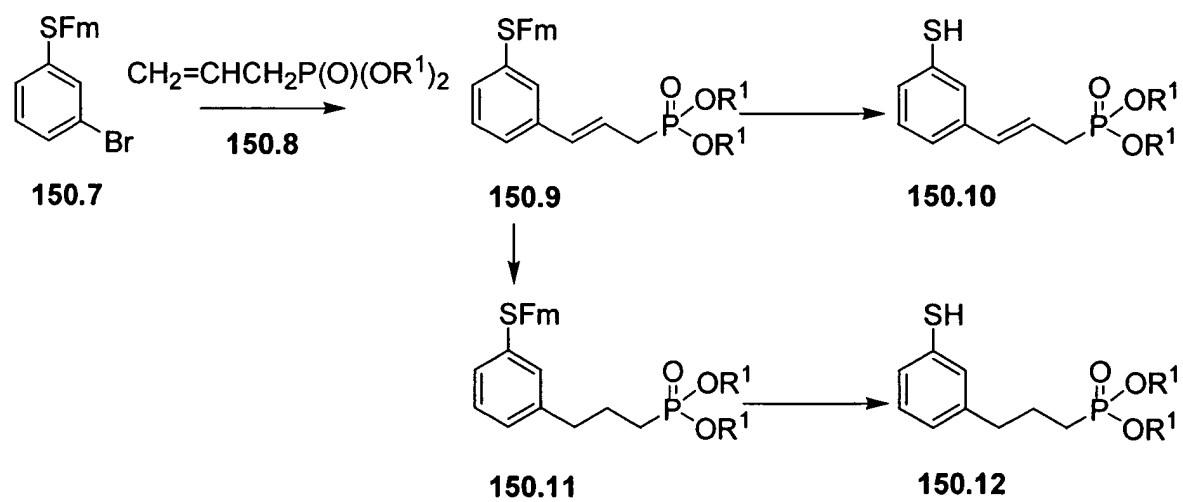


## Scheme 150

### Method

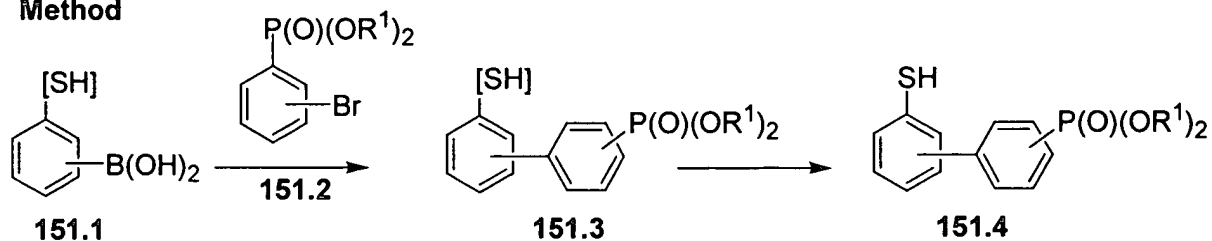


### Example

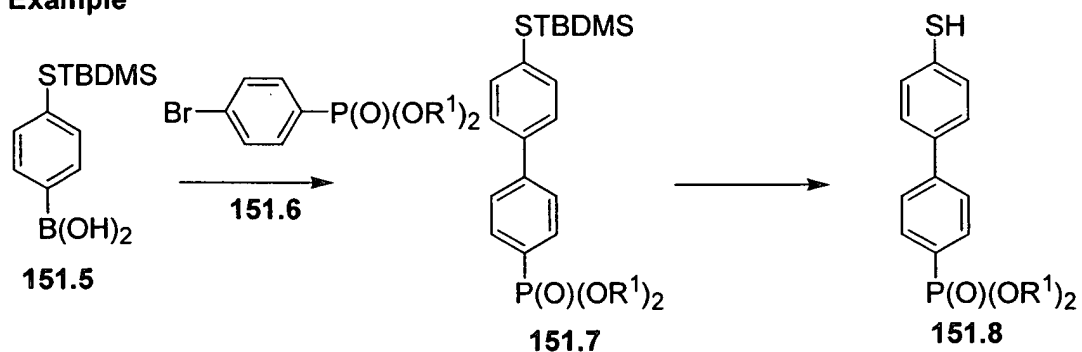


## Scheme 151

### Method

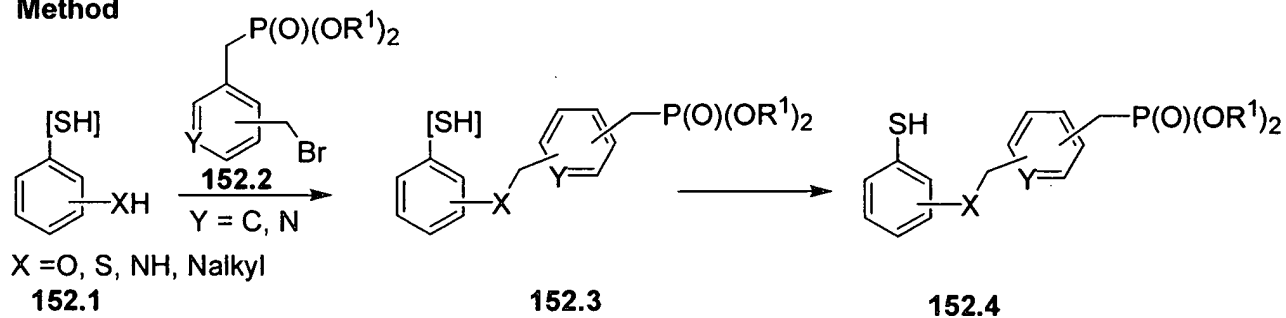


### Example

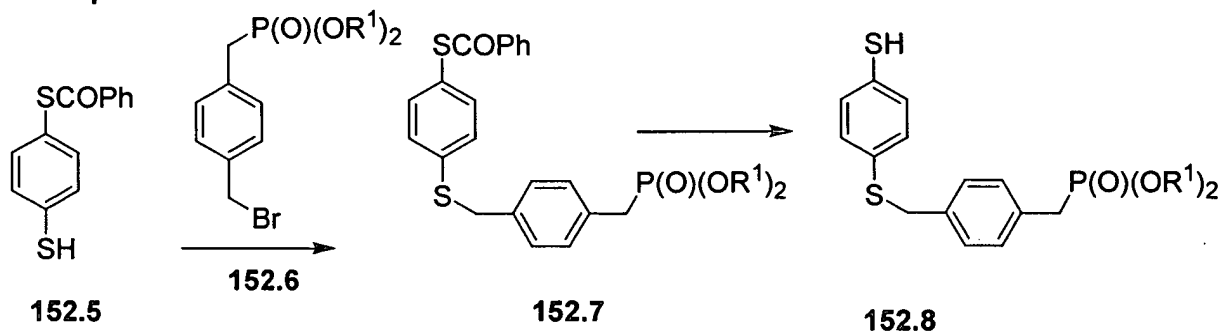


## Scheme 152

### Method

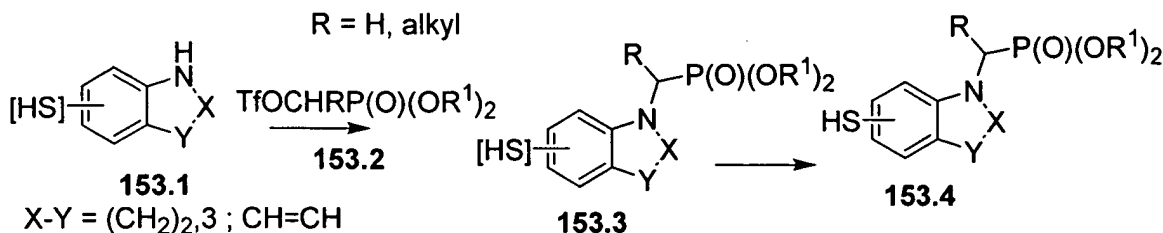


### Example

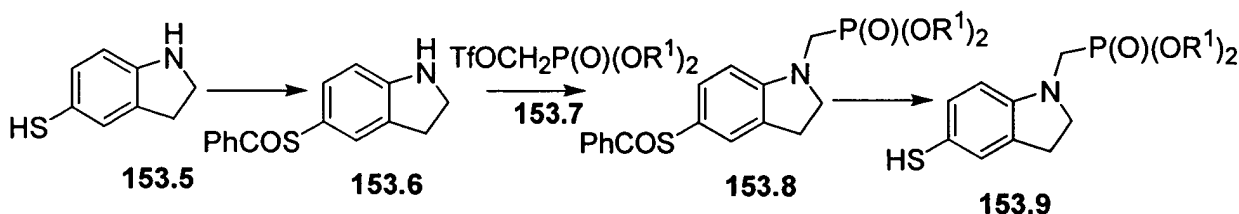


## Scheme 153

### Method



### Example



## Preparation of tert-butylamine derivatives 9.3 and 25.4 incorporating phosphonate groups

Schemes 154 – 158 illustrate the preparation of the tert. butylamine derivatives 9.3 and 25.4 in which the substituent A is either the group link P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor, such as [OH], [SH], Br, which are employed in the preparation of the intermediate phosphonate esters 3, 7, 11 and 20.

Scheme 154 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethyl bromide 154.1 is reacted with a trialkyl phosphite 154.2, under the conditions of the Arbuzov reaction, as described in Scheme 137, to afford the phosphonate 154.3, which is then deprotected to give the amine 154.4.

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide 154.6, is heated with a trialkyl phosphite at ca 150°C to afford the product 154.7. Deprotection then affords the free amine 154.8. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion is effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group is removed by treatment of the substrate with triethylsilane, triethylamine and a catalytic amount of palladium (II) chloride, as described in *Chem. Ber.*, 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as

described in *J. Chem. Soc.*, Perkin Trans. I, 1277, 1988. The cbz group is also removed by treatment with Lewis acid such as boron tribromide, as described in *J. Org. Chem.*, 39, 1247, 1974, or aluminum chloride, as described in *Tetrahedron Lett.*, 2793, 1979.

Using the above procedures, but employing different trialkyl phosphites, there are obtained the corresponding amines **154.4**.

Scheme **155** illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. A protected alcohol or thiol **155.1** is reacted with a dialkyl bromoalkylphosphonate **155.2**, to afford the displacement product **155.3**. Deprotection, if needed, then yields the amine **155.4**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **155.5** is reacted with a dialkyl 4-bromobutyl phosphonate **155.6**, prepared as described in *Synthesis*, 1994, 9, 909, in dimethylformamide containing potassium carbonate and a catalytic amount of potassium iodide, at ca 60° to afford the phosphonate **155.7**. Deprotection, by hydrogenation over a palladium catalyst, then affords the free amine **155.8**.

Using the above procedures, but employing different alcohols or thiols **155.1**, and/or different bromoalkylphosphonates **155.2**, there are obtained the corresponding ether and thioether products **155.4**.

Scheme **156** describes the preparation of carbon-linked tert. butylamine phosphonate derivatives, in which the carbon chain is unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine **156.1** is reacted, under basic conditions, with a dialkyl chlorophosphite **156.2**, to afford the acetylenic phosphonate **156.3**. The coupled product **156.3** is deprotected to afford the amine **156.4**. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **156.5** and **156.6** respectively.

For example, 2-amino-2-methylprop-1-yne **156.7**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **156.8**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°C. The resultant anion is then reacted with a dialkyl chlorophosphite **156.2** to afford the phosphonate **156.9**. Deprotection, for example by treatment with hydrazine, as described in *J. Org. Chem.*, 43, 2320, 1978, then affords the free amine **156.10**. Partial

catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate **156.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **156.12**.

Using the above procedures, but employing different acetylenic amines **156.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **156.4**, **156.5** and **156.6**.

Scheme **157** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

In this method, an aminopropyl-substituted cyclic amine **157.1** is reacted with a limited amount of a bromoalkyl phosphonate **157.2**, using, for example, the conditions described above (Scheme **149**) to afford the displacement product **157.3**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **157.4**, the preparation of which is described in *Chem. Pharm. Bull.*, 1994, 42, 1442, is reacted with one molar equivalent of a dialkyl 4-bromobutyl phosphonate **157.5**, prepared as described in *Synthesis*, 1994, 9, 909, to afford the displacement product **157.6**.

Using the above procedures, but employing, in place of 3-(1-amino-1-methyl)ethylpyrrolidine **157.4**, different cyclic amines **157.1**, and/or different bromoalkylphosphonates **157.2**, there are obtained the corresponding products **157.3**.

Scheme **158** illustrates the preparation of the amides **9.3** which are employed in the preparation of the phosphonate esters **3**. In this procedure, the carboxylic acids **158.1**, the structures of which are illustrated in Chart **10**, compounds **C1 - C16**, are converted into the BOC-protected derivatives **155.8**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine is reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like. The carboxylic acid **158.2** is then coupled, as described in Scheme **1**, with the tert. butylamine derivatives **25.4**, or precursors thereto, the preparation of which is described in Schemes **154 - 157**, to afford the amide **158.3**. The BOC group is then removed to yield the amine **9.3**. The removal of BOC

protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

### **Preparation of pyridine intermediates 13.1 incorporating phosphonate substituents**

Schemes 159 - 163, described the preparation of chloromethyl or formyl pyridine derivatives incorporating phosphonate moieties. Scheme 164 illustrates the conversion of the above compounds into the piperazine derivatives 13.1 which are employed in the preparation of the phosphonate esters 4.

Scheme 159 illustrates the preparation of chloromethyl-substituted pyridines in which a phosphonate moiety is directly attached to the pyridine ring.

In this procedure, a halo-substituted methylpyridine 159.1 is reacted with a dialkyl phosphite 159.2, to afford the phosphonate product 159.3. The coupling reaction is conducted in the presence of a palladium (0) catalyst, for example as described in *J. Med. Chem.*, 35, 1371, 1992. The product 159.3 is then converted into the chloromethyl derivative 159.4 by means of a chlorination reaction. The chlorination of benzylic methyl groups is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. A variety of free-radical chlorinating agents are employed.

For example, 3-bromo-5-methylpyridine, 159.5 (ChemPacific) is reacted with an equimolar amount of a dialkyl sodium phosphite, 13.2 in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, in toluene at reflux, to yield the phosphonate 159.6. The latter compound is then chlorinated, for example by the use of one molar equivalent of phenyliodonium dichloride, as described in *J. Org. Chem.*, 29, 3692, 1964, to prepare the chloromethyl compound 159.7.

Using the above procedures, but employing, in place of the bromomethyl pyridine 159.5, different halomethyl pyridines 159.1, and/or different dialkyl phosphites 159.2 the corresponding products 159.4 are obtained.

Scheme 160 depicts the preparation of chloromethyl pyridines incorporating a phosphonate group attached to the pyridine ring by means of a carbon link. In this procedure, a bis(chloromethyl)pyridine 160.1 is reacted with a sodium dialkyl phosphite 146.3, employing,

for example, procedures described in *J. Med. Chem.*, 35, 1371, 1992, to afford the displacement product **160.2**.

For example, 3,5-bis(chloromethyl)pyridine **160.3**, the preparation of which is described in *Eur. J. Inorg. Chem.*, 1998, 2, 163, is reacted with one molar equivalent of a dialkyl sodium phosphite **146.3** in tetrahydrofuran, at ambient temperature, to afford the product **160.4**.

Using the above procedures, but employing, in place of the bis(chloromethyl) compound **160.3**, different bis(chloromethyl) pyridines **160.1**, and/or different dialkyl sodium phosphites **146.3** the corresponding products **160.2** are obtained.

Scheme **161** illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine nucleus by means of a saturated or unsaturated carbon chain. In this procedure, a suitably protected halo-substituted pyridine carboxaldehyde **161.1** is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme **150**, with a dialkyl alkenyl phosphonate **161.2**. Methods for the protection of aldehydes are described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 175. The protected aldehyde **161.1** is reacted with an olefinic phosphonate **161.2**, in the presence of a palladium (0) catalyst, to afford the coupled product **161.3**. Deprotection of the aldehyde group then affords the product **161.6**. Alternatively, the unsaturated compound **161.3** is reduced to afford the saturated analog **161.5**, which upon deprotection yields the saturated analog **161.7**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide.

For example, 5-bromopyridine-3-carboxaldehyde **161.8** (ChemPacific) is converted into the dimethyl acetal, by reaction with methanolic ammonium chloride, as described in *J. Org. Chem.*, 26, 1156, 1961. The acetal **161.9** is then reacted with a dialkyl butenyl phosphonate **161.10**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371, to afford the coupled product **161.11**. Deprotection, for example by treatment with formic acid in pentane, as described in *Synthesis*, 651, 1983, yields the free aldehyde **161.13**. The product is reduced, for example by reaction with diimide, as described in *J. Org. Chem.*, 30, 3965, 1965, to afford the saturated product **161.12**.

Using the above procedures, but employing, in place of the aldehyde **161.8**, different aldehydes **161.1**, and/or different phosphonates **161.2**, the corresponding products **161.6** and **161.7** are obtained.

Scheme **162** illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine by a heteroatom and a carbon chain. In this procedure, a 2- or 4-halo-substituted pyridine aldehyde **162.1** is reacted with a dialkyl hydroxy- or thio-alkylphosphonate **162.2**. The preparation of alkoxypyridines by the reaction of alkoxides with halopyridines is described, for example, in *J. Am. Chem. Soc.*, 82, 4414, 1960. The preparation of pyridine thioethers by reaction of halopyridines with thiols is described, for example, in *Chemistry of Heterocyclic Compounds*, Pyridine and its derivatives, E. Klingsberg, Ed, part 4, p. 358. The alcohols and thiols are transformed into metal salts, for example sodium or potassium salts, and then reacted with the halopyridine substrates at elevated temperatures, optionally in the presence of copper powder catalyst, to afford the ether or thioether products **162.3**.

For example, a tetrahydrofuran solution of 2-bromo-pyridine-5-aldehyde **162.4**, prepared as described in *Tetrahedron Lett.*, 2001, 42, 4841, is heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphosphonate **162.5**, the preparation of which is described in *Aust. J. Chem.*, 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **162.6**.

Using the above procedures, but employing, in place of the haloaldehyde **162.4**, different haloaldehydes **162.1**, and/or different hydroxy or thio-alkyl phosphonates **162.2**, the corresponding products **162.3** are obtained.

Scheme **163** depicts the preparation of pyridine aldehydes **163.3** in which the phosphonate group is attached to the pyridine nucleus by means of a chain incorporating a nitrogen atom. In this procedure, a pyridine dicarboxaldehyde **163.1** is reacted with a dialkyl aminoalkyl phosphonate **163.2**, in the presence of a reducing agent, so as to effect a reductive amination reaction, yielding the product **163.3**. The preparation of amines by means of reductive amination of aldehydes is described, for example, in *Advanced Organic Chemistry*, F. A. Carey, R. J. Sundberg, Plenum, 2001, part B, p. 269. The reactants are combined in an inert solvent such as an alcohol or ether, and treated with a reducing agent such as, for example, sodium cyanoborohydride or sodium triacetoxy borohydride, so as to yield the amine product **163.3**.

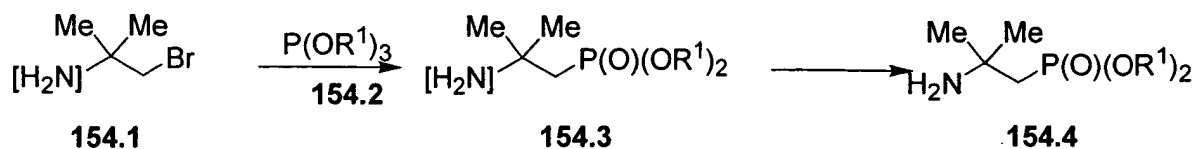
For example, equimolar amounts of pyridine 3,5-dicarboxaldehyde **163.4**, prepared as described in *Tetrahedron Lett.*, 1994, 35, 6191, and a dialkyl 2-aminoethyl phosphonate **163.5** prepared as described in *J. Org. Chem.*, 2000, 65, 676, are reacted with sodium cyanoborohydride in isopropanol containing acetic acid, at ambient temperature, so as to produce the amine product **163.6**

Using the above procedures, but employing, in place of the dicarboxaldehyde **163.4**, different dicarboxaldehydes **163.1**, and/or different aminoalkyl phosphonates **163.2**, the corresponding products **163.3** are obtained.

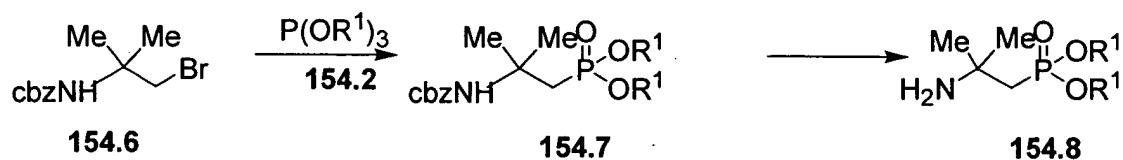
Scheme **164** illustrates the incorporation of the formyl or chloromethyl pyridines, the syntheses of which are described above, into the piperazine reagent **13.1**. Compounds **164.2** in which Z is chloromethyl are reacted with the mono-protected piperazine derivatives **164.1**, the preparation of which are described in WO 9711698, to afford the alkylated product **164.3**. The preparation of amines by means of alkylation reactions is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 397. Equimolar amounts of the reactants **164.1** and the halomethyl pyridine compound **164.2**, are combined in a organic solvent such as an alcohol or dimethylformamide, in the presence of a base such as triethylamine or potassium carbonate, to give the alkylated products **164.3**. The alkylation of a piperazine derivative by a 3-chloromethylpyridine is described in WO9628439. Alternatively, the amine **164.1** is reacted with the aldehyde **164.2** to afford the product **164.3** in a reductive alkylation reaction. The preparation of amines by means of reductive amination procedures is described in Scheme **163**. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The reductive alkylation reaction between 3-pyridinecarboxaldehyde and a substituted piperazine is described in WO9628439. Deprotection of the product **164.3** then yields the free amine **13.1**.

# Scheme 154

## Method

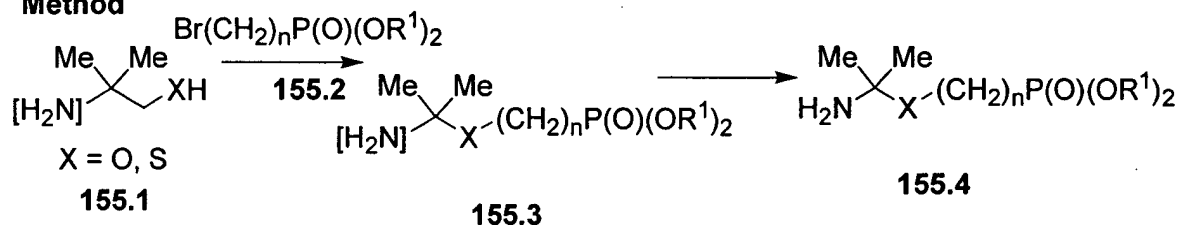


## Example

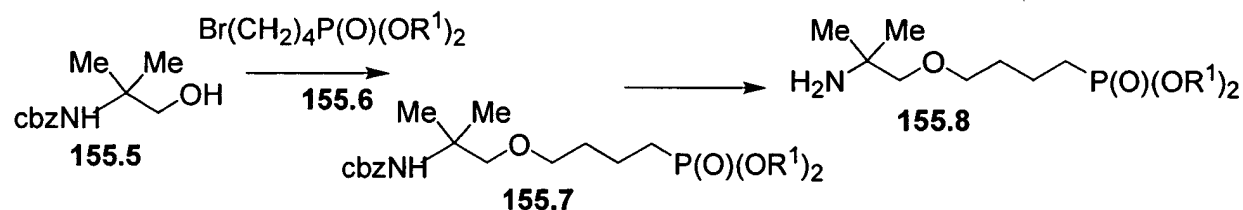


# Scheme 155

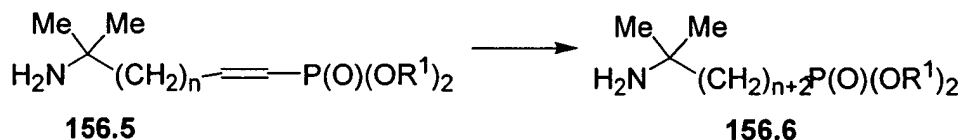
## Method



## Example

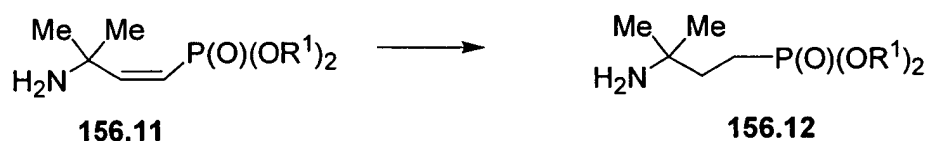


## Method

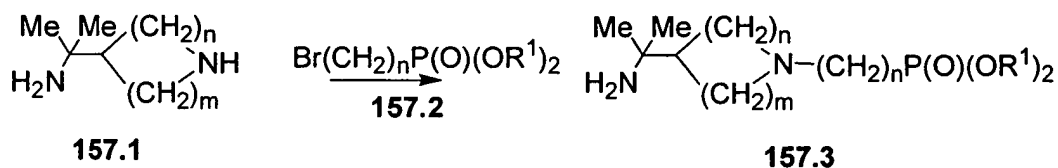


**Example 1**

156.7      156.8      156.9      156.10  
phth = phthalimido

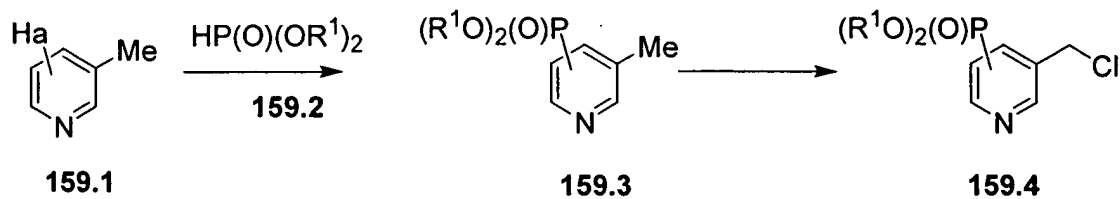


## Method

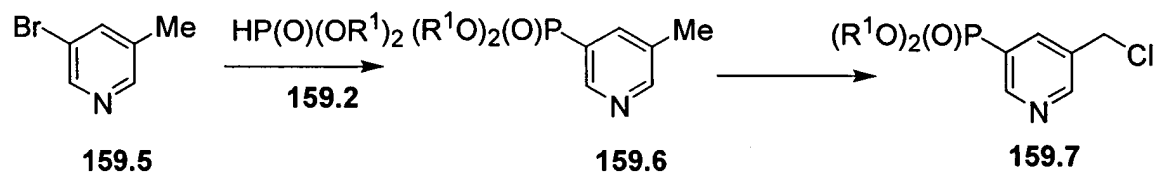


# Scheme 159

## Method

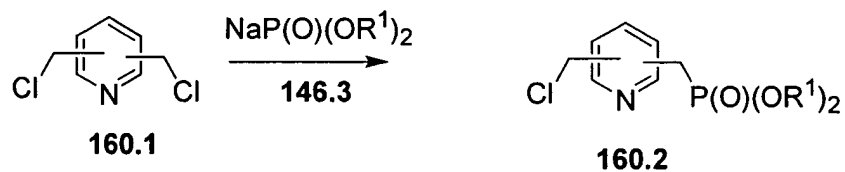


## Example

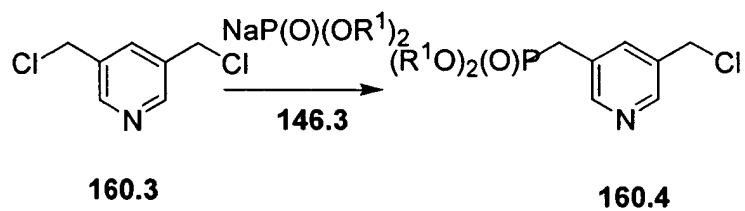


# Scheme 160

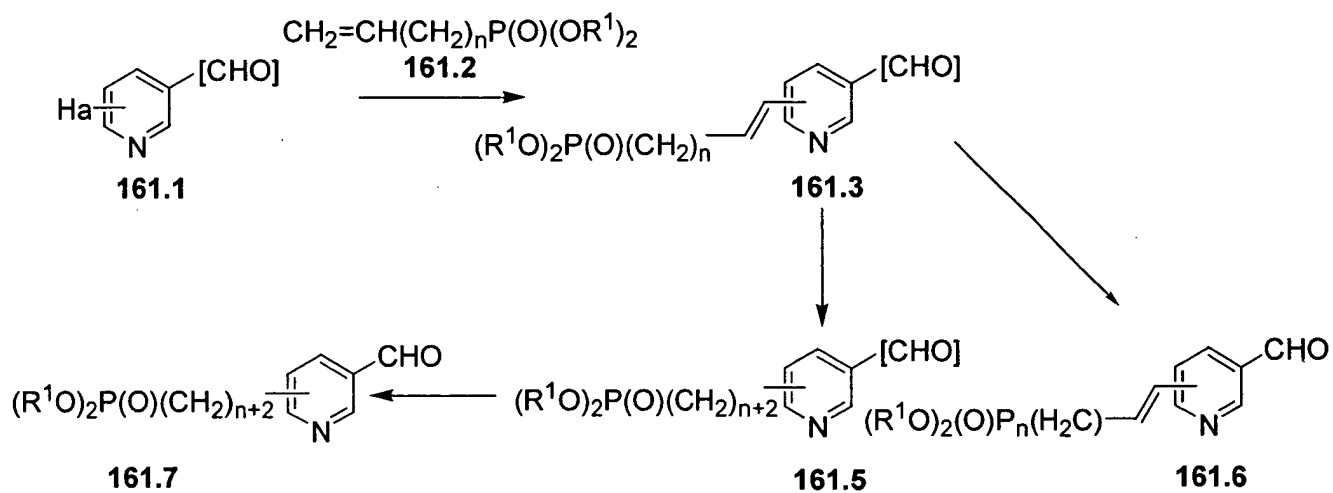
## Method



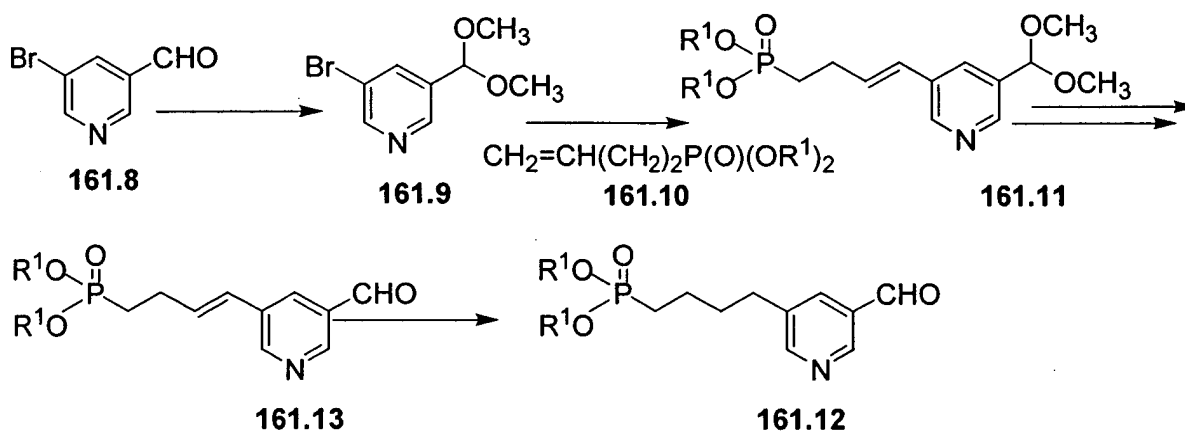
## Example



**Scheme 161**  
**Method**

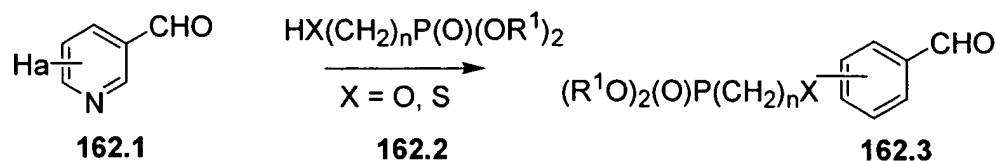


**Example**

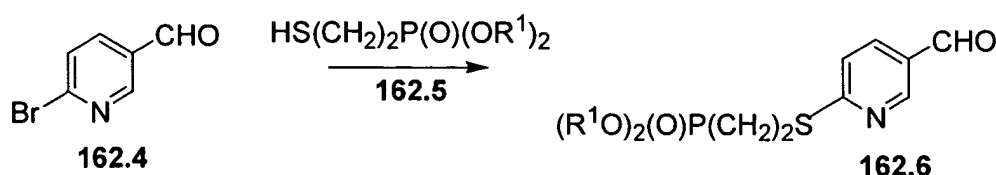


### Scheme 162

#### Method

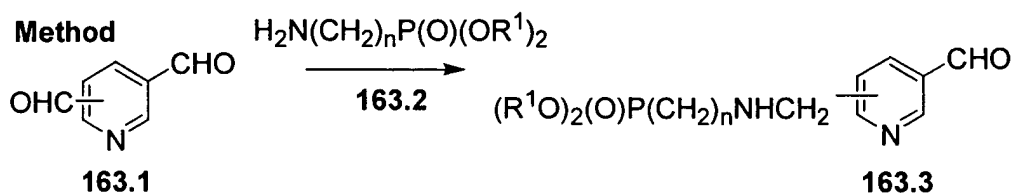


#### Example

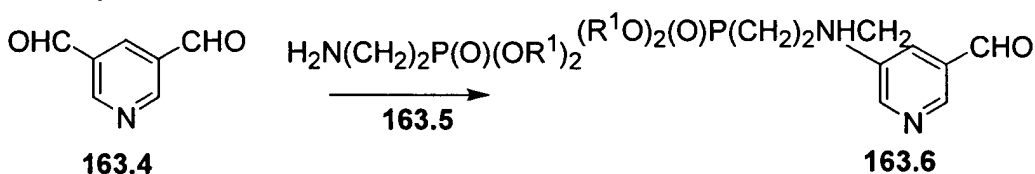


### Scheme 163

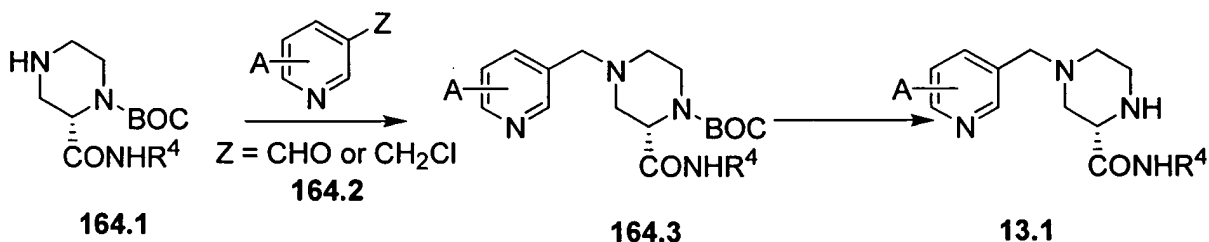
#### Method



#### Example



### Scheme 164



### Preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups

Schemes 165 - 169 illustrate the preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups, which are employed in the synthesis of the phosphonate esters 6 and 13.

Scheme 165 depicts the preparation of dimethoxybenzyl alcohols in which the phosphonate group is attached either directly to the phenyl ring or by a saturated or unsaturated

alkylene chain. In this procedure, a bromo-substituted dimethoxy benzyl alcohol is coupled, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate **165.2**, to afford the coupled product **165.3**. The reaction is conducted under the conditions described in Scheme **150**. The product **165.3** is then reduced, for example by treatment with diimide, as described in Scheme **150**, to yield the saturated analog **165.4**. Alternatively, the bromo compound **165.1** is coupled, in the presence of a palladium catalyst, as described in Scheme **144**, with a dialkyl phosphite **165.5**, to afford the phosphonate **165.6**.

For example, 4-bromo-3,5-dimethoxybenzyl alcohol **165.7**, the preparation of which is described in *J. Med. Chem.*, 1977, 20, 299, is coupled with a dialkyl allyl phosphonate **165.8** (Aldrich) in the presence of bis(triphenylphosphine) palladium (II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **165.9**. The product is reduced, for example by treatment with diimide, as described in *J. Org. Chem.*, 52, 4665, 1987, to yield the saturated compound **165.10**.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol **165.7**, different benzyl alcohols **165.1**, and/or different alkenyl phosphonates **165.2**, the corresponding products **165.3** and **165.4** are obtained.

As a further example, 3-bromo-4,5-dimethoxybenzyl alcohol **165.11**, the preparation of which is described in *J. Org. Chem.*, 1978, 43, 1580, is coupled, in toluene solution at reflux, with a dialkyl phosphite **165.5**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in *J. Med. Chem.*, 35, 1371, 1992, to yield the phenyl phosphonate **165.12**.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol **165.11**, different benzyl alcohols **165.1**, and/or different dialkyl phosphites **165.5**, the corresponding products **165.6** are obtained.

Scheme **166** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted dimethoxybenzyl alcohol **166.1** is coupled, as described in Scheme **1**, with a dialkyl aminoalkyl phosphonate **166.2** to prepare the amide **166.3**.

For example, 2,6-dimethoxy-4-(hydroxymethyl)benzoic acid **166.4**, the preparation of which is described in *Chem. Pharm. Bull.*, 1990, 38, 2118, is coupled in dimethylformamide solution, in the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate

**166.5**, the preparation of which is described in *J. Org. Chem.*, 2000, 65, 676, to afford the amide **166.6**.

Using the above procedures, but employing, in place of the dimethoxybenzoic acid **166.4**, different benzoic acids **166.1**, and/or different aminoalkyl phosphites **166.2**, the corresponding products **166.3** are obtained.

Scheme **167** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an aminoalkyl or an amide group. In this procedure, an amino-substituted dimethoxybenzyl alcohol **167.1** is reacted, under reductive amination conditions, as described in Scheme **163**, with a dialkyl formylalkylphosphonate **167.2** to yield the aminoalkyl product **167.3**. Alternatively, the amino-substituted dimethoxybenzyl alcohol **167.1** is coupled, as described in Scheme **1**, with a dialkyl carboxyalkyl phosphonate **167.4**, to produce the amide **167.5**.

For example, 3-amino-4,5-dimethoxybenzyl alcohol **167.6**, the preparation of which is described in *Bull. Chem. Soc. Jpn.*, 1972, 45, 3455, is reacted, in the presence of sodium triacetoxyborohydride, with a dialkyl formylmethyl phosphonate **167.7**, as described in Scheme **135**, to afford the aminoethyl phosphonate **167.8**.

Using the above procedures, but employing, in place of the amine **167.6**, different amines **167.1**, and/or different formylalkyl phosphites **167.2**, the corresponding products **167.3** are obtained.

As a further example, 4-amino-3,5-dimethoxybenzyl alcohol **167.9**, the preparation of which is described in *Bull. Chem. Soc. Jpn.*, 1972, 45, 3455, is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl phosphonoacetic acid **167.10**, (Aldrich) to afford the amide **167.11**.

Using the above procedures, but employing, in place of the amine **167.6**, different amines **167.1**, and/or different carboxyalkyl phosphonates **167.4**, the corresponding products **167.5** are obtained.

Scheme **168** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an alkoxy group. In this procedure, a dimethoxyhydroxy benzyl alcohol **168.1** is reacted with a dialkyl alkylphosphonate **168.2** with a terminal leaving group to afford the alkoxy product **168.3**. The alkylation reaction is effected in

a polar organic solvent such as dimethylformamide in the presence of a base such as dimethylaminopyridine or cesium carbonate.

For example, 4-hydroxy-3,5-dimethoxybenzyl alcohol **168.4**, the preparation of which is described in *J. Med. Chem.* 1999, 43, 3657, is reacted in dimethylformamide at 80°C with an equimolar amount of a dialkyl bromopropyl phosphonate **168.5**, prepared as described in *J. Am. Chem. Soc.*, 2000, 122, 1554, and cesium carbonate, to give the alkylated product **168.6**.

Using the above procedures, but employing, in place of the phenol **168.4**, different phenols **168.1**, and/or different alkyl phosphonates **168.2**, the corresponding products **168.3** are obtained.

As a further example, 4,5-dimethoxy-3-hydroxybenzyl alcohol **168.7**, prepared as described in *J. Org. Chem.*, 1989, 54, 4105, is reacted, as described above, with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **168.8**, prepared as described in *Tetrahedron Lett.*, 1986, 27, 1477, to produce the alkylated product **168.9**.

Using the above procedures, but employing, in place of the phenol **168.7**, different phenols **168.1**, and/or different alkyl phosphonates **168.2**, the corresponding products **168.3** are obtained.

Scheme **169** illustrates the conversion of the benzyl alcohols **169.1**, in which the substituent A is the group link-P(O)(OR<sup>1</sup>)<sub>2</sub>, or a precursor, prepared as described above, into the corresponding halides **169.2**. The conversion of alcohols into chlorides, bromides and iodides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff, p. 356ff and p. 358ff. For example, benzyl alcohols are transformed into the chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in *J. Am. Chem. Soc.*, 106, 3286, 1984. Benzyl alcohols are transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in *J. Am. Chem. Soc.*, 92, 2139, 1970. Benzyl alcohols are transformed into iodides by reaction with sodium iodide and boron trifluoride etherate, as described in *Tetrahedron Lett.*, 28, 4969, 1987, or by reaction with diphosphorus tetraiodide, as described in *Tetrahedron Lett.*, 1801, 1979. Benzylic chlorides or bromides are transformed into the corresponding iodides by reaction with sodium iodide in acetone or methanol, for example as described in EP 708085.

### Preparation of dimethoxythiophenols 23.1 incorporating phosphonate groups

Schemes 170 - 173 illustrate the preparation of the dimethoxythiophenols 23.1 incorporating phosphonate groups, which are used in the synthesis of the phosphonate esters 6 and 13.

Scheme 170 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of an amide group. In this procedure, a dimethoxyamino-substituted benzoic acid 170.1 is converted into the corresponding thiol 170.2. The conversion of amines into the corresponding thiols is described in *Sulfur Lett.*, 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoborate, is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in *Sulfur Lett.*, 2000, 24, 123, to afford the thiol 170.2. The product is then coupled, as described above, with a dialkyl aminoalkyl phosphonate 170.3, to yield the amide 170.4.

For example, 5-amino-2,3-dimethoxybenzoic acid 170.5, the preparation of which is described in JP 02028185, is converted, as described above, into 2,3-dimethoxy-5-mercaptobenzoic acid 170.6. The product is then coupled, as described in Scheme 1, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate 170.7, (Acros) to afford the amide 170.8.

Using the above procedures, but employing, in place of the amine 170.5, different amines 170.1, and/or different aminoalkyl phosphonates 170.3, the corresponding products 170.4 are obtained.

Scheme 171 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromodimethoxyaniline 171.1 is converted, as described in Scheme 170, into the corresponding thiophenol 171.2. The thiol group is then protected to give the derivative 171.3. The protection and deprotection of thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl

chloride in the presence of ammonium hydroxide, as described in *Bull. Chem. Soc. Jpn.*, 37, 433, 1974. The product **171.3** is then coupled, in the presence of a palladium catalyst, as described in Scheme **165**, with a dialkyl alkenyl phosphonate **171.4**, to give the alkenyl product **171.5**.

Deprotection then yields the thiol **171.6**. Reduction of the double bond, for example by reaction with diimide, as described in *J. Org. Chem.*, 52, 4665, 1987, affords the saturated product **171.7**.

For example, 4-bromo-3,5-dimethoxyaniline **171.8**, prepared as described in WO9936393, is converted, by diazotization, into 4-bromo-3,5-dimethoxythiophenol **171.9**. The product is then transformed into the S-benzoyl derivative **171.10**, by reaction with benzoyl chloride in pyridine, and the product is coupled, as described in Scheme **165**, with a dialkyl butenyl phosphonate **171.11**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, to yield the phosphonate **171.12**. Deprotection, for example by treatment with aqueous ammonia at ambient temperature, as described in *J. Am. Chem. Soc.*, 85, 1337, 1963, then afford the thiol **171.13**. The double bond is reduced with diimide to give the saturated analog **171.14**.

Using the above procedures, but employing, in place of the amine **171.8**, different amines **171.1**, and/or different alkenyl phosphonates **171.4**, the corresponding products **171.6** and **171.7** are obtained.

Scheme **172** illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group directly attached to the phenyl ring. In this procedure, a protected bromodimethoxythiophenol **172.1**, prepared, for example, from the corresponding aniline, as described above, is coupled, in the presence of a palladium catalyst, as described in Scheme **165**, with a dialkyl phosphite **172.2**. The product is then deprotected to afford the phosphonate ester **172.4**.

For example, 3-bromo-4,5-dimethoxyaniline **172.5**, prepared as described in DE 2355394, is converted, as described above in Schemes **165** and **171**, into S-benzoyl 3-bromo-4,5-dimethoxythiophenol **172.6**. This compound is then coupled, in toluene solution at reflux, with a dialkyl phosphite **172.2**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in *J. Med. Chem.*, 35, 1371, 1992, to yield the phenyl phosphonate **172.7**. Deprotection, as described in Scheme **171**, then affords the thiol **172.8**.

Using the above procedures, but employing, in place of the protected thiol **172.6**, different thiol **172.1**, the corresponding products **172.4** are obtained.

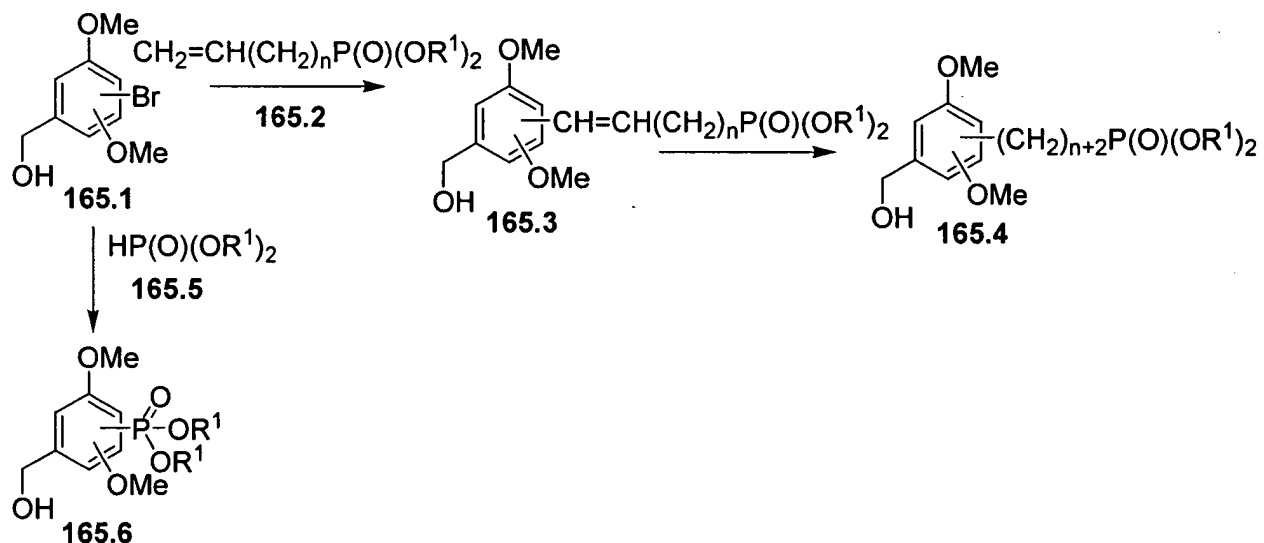
Scheme 173 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached to the phenyl ring by means of an alkoxy group. In this procedure, a dimethoxy aminophenol 173.1 is converted, via the diazo compound, into the corresponding thiophenol 173.2. The thiol group is then protected, and the product 173.3 is alkylated, as described in Scheme 168, with a dialkyl bromoalkyl phosphonate 173.4. Deprotection of the product 173.5 then affords the thiophenol 173.6.

For example, 5-amino-2,3-dimethoxyphenol 173.7, prepared as described in WO 9841512, is converted by diazotization, as described above, into the thiophenol 173.8, and the product is protected by reaction with one molar equivalent of benzoyl chloride in pyridine, to yield the S-benzoyl product 173.9. The latter compound is then reacted, in dimethylformamide solution at 80°C, with a dialkyl bromoethyl phosphonate 173.10 (Aldrich) and cesium carbonate, to produce the ethoxyphosphonate 173.11. Deprotection, as described in Scheme 171, then yields the thiol 173.12.

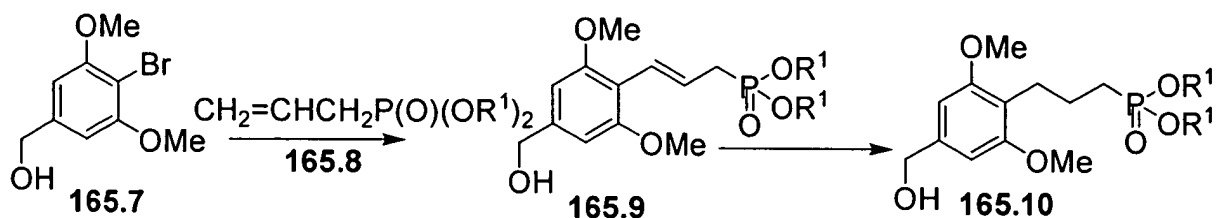
Using the above procedures, but employing, in place of the thiol 173.8, different thiol 173.2, and/or different bromoalkyl phosphonates 173.4, the corresponding products 173.6 are obtained.

#### Scheme 165

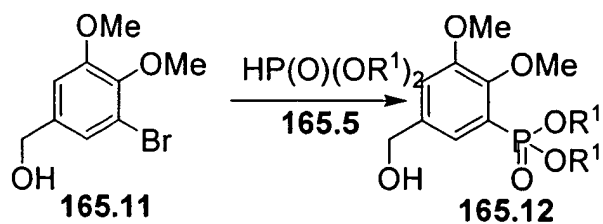
##### Method



### Example 1

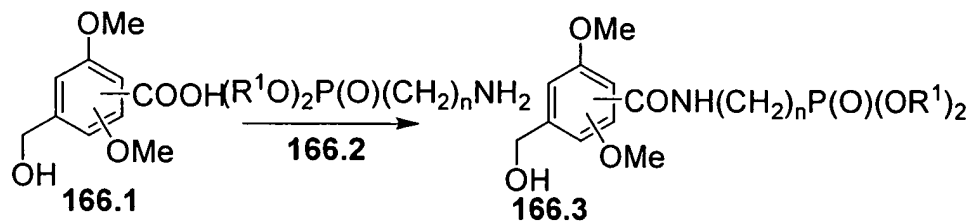


### Example 2

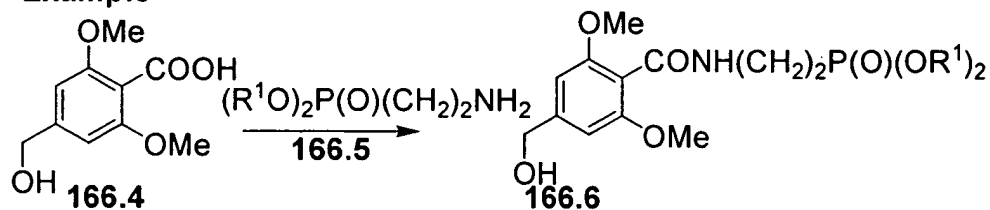


## Scheme 166

### Method

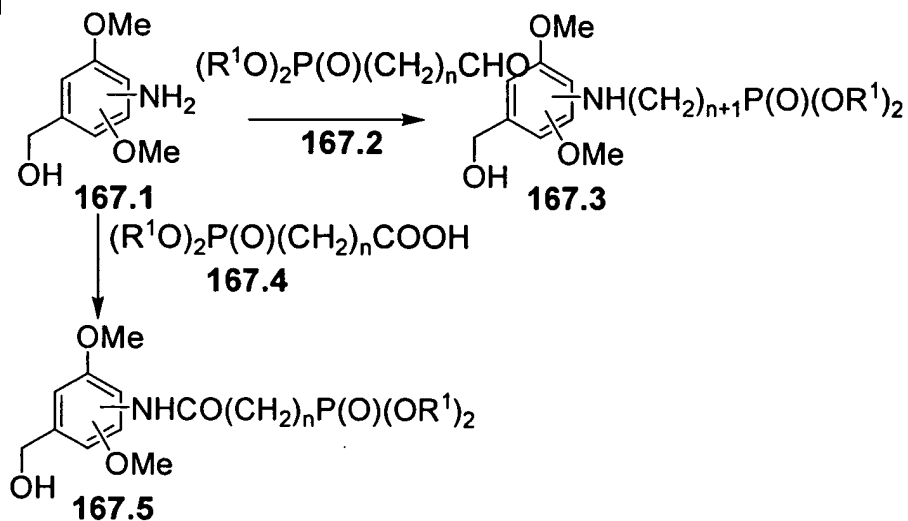


### Example

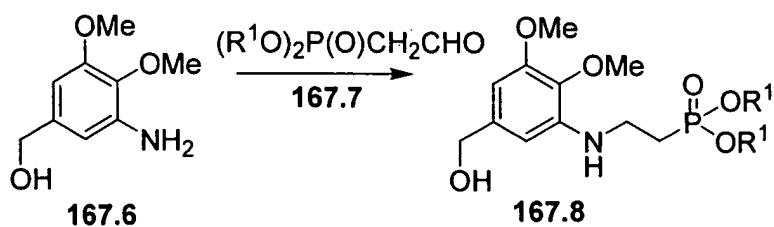


## Scheme 167

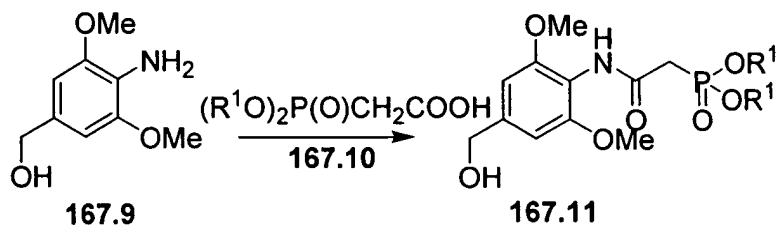
### Method



### Example 1

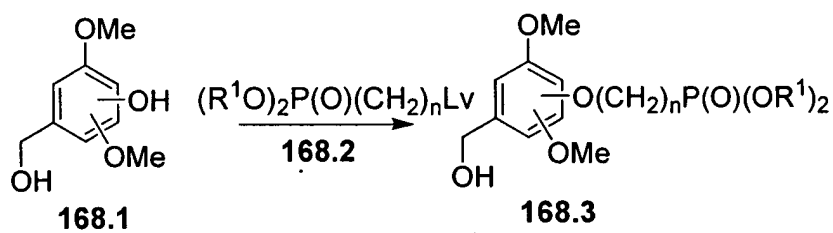


### Example 2

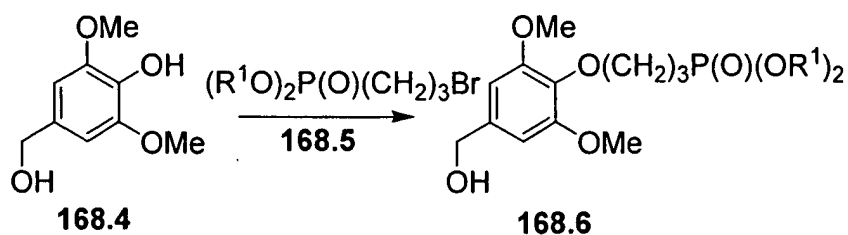


### Scheme 168

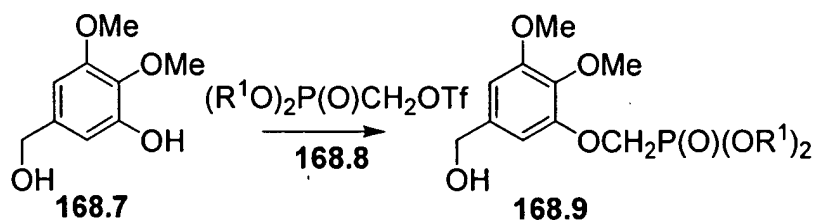
#### Method



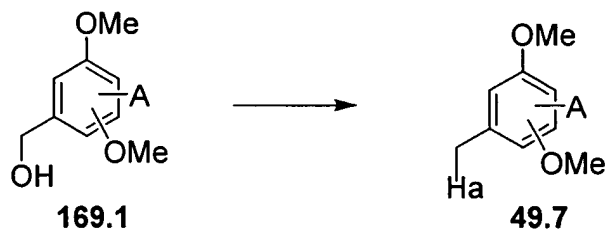
### Example 1



### Example 2

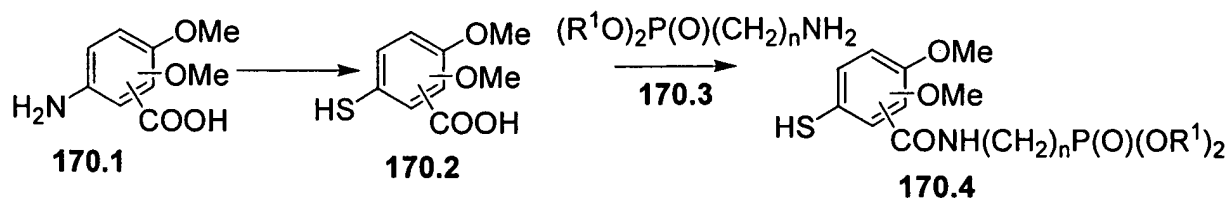


### Scheme 169

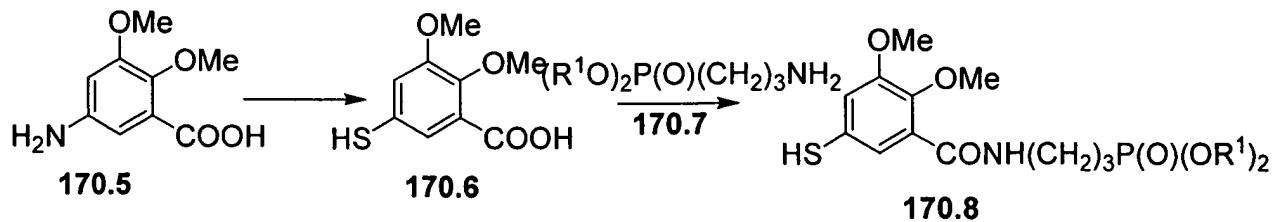


### Scheme 170

#### Method

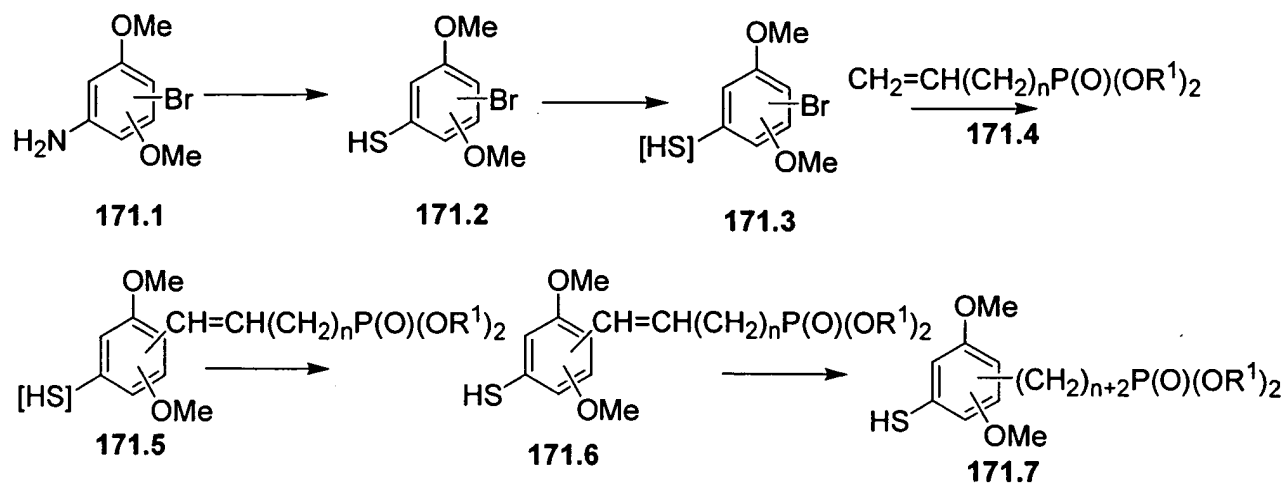


### Example 1

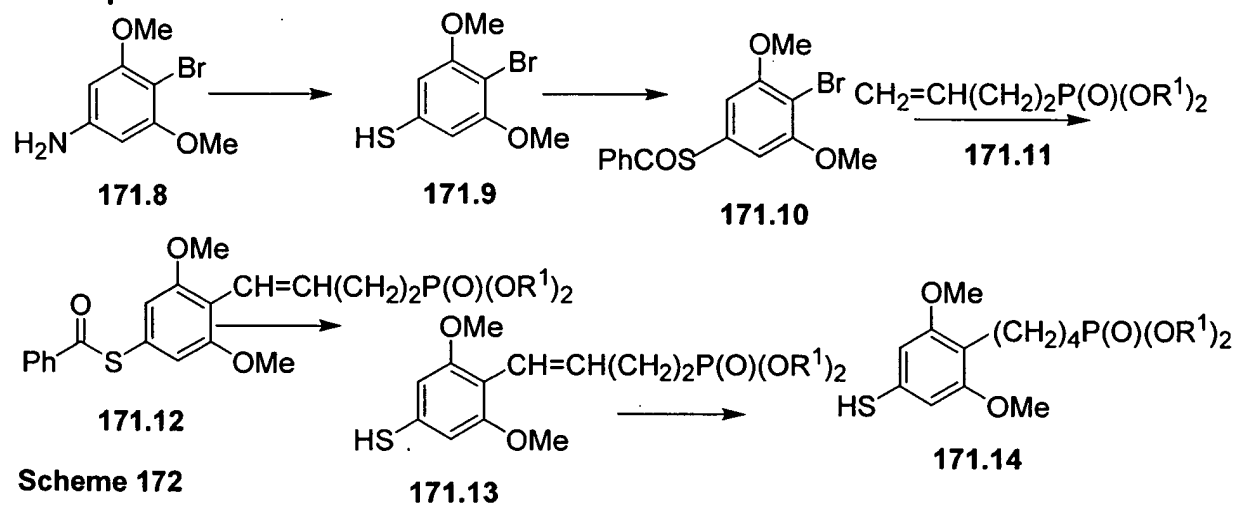


# Scheme 171

## Method

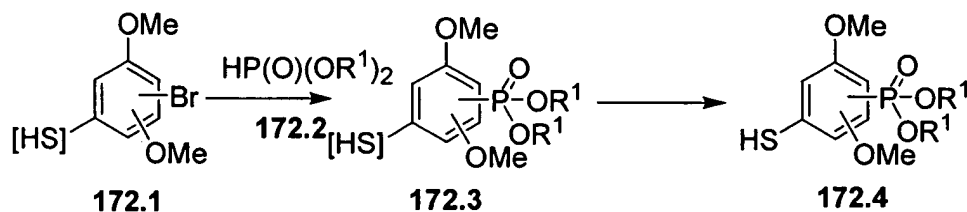


## Example

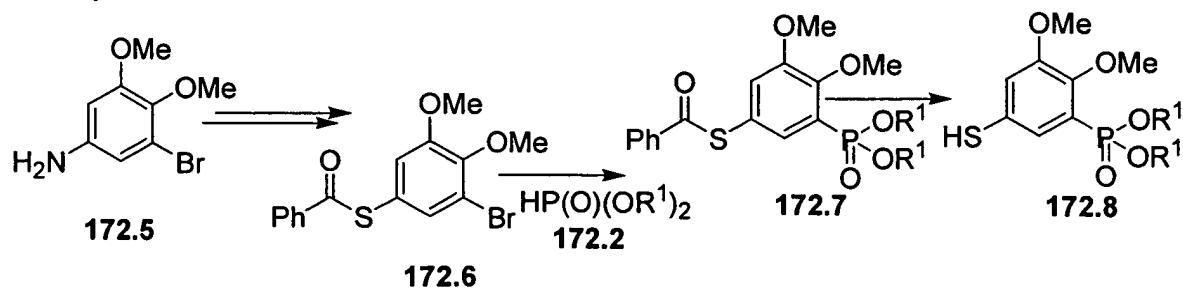


# Scheme 172

## Method

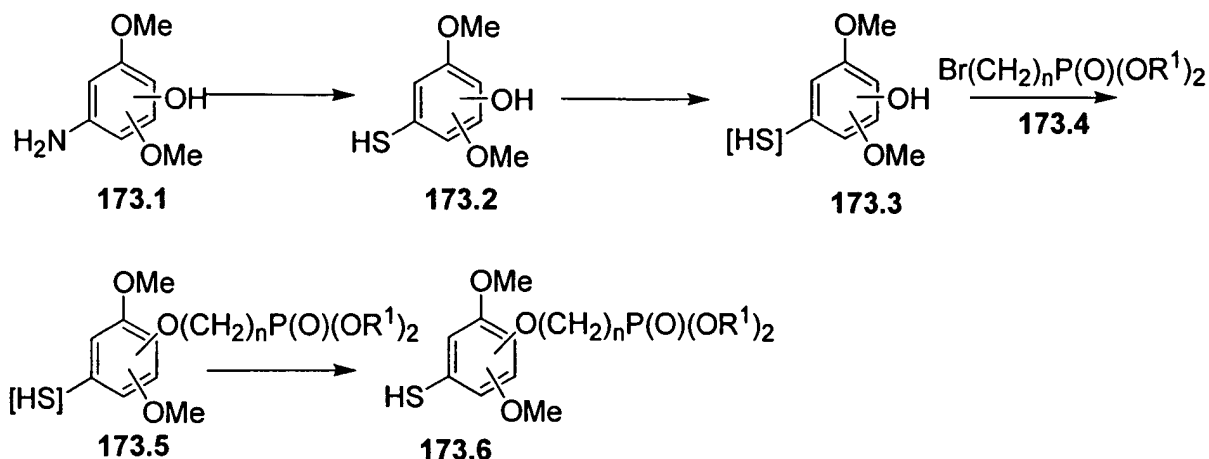


## Example

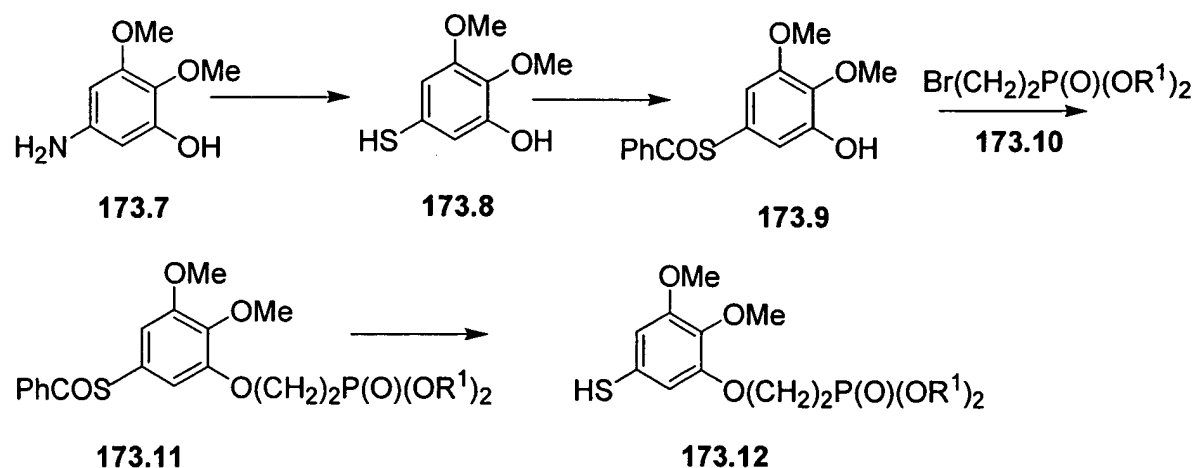


### Scheme 173

#### Method



#### Example



### Preparation of ethanolamine derivatives 29.1 incorporating phosphonate groups

Schemes 174 - 178 illustrate the preparation of the ethanolamine derivatives 29.1 which are employed in the preparation of the phosphonate esters 18 and 8.

Scheme 174 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkyl chain. In this procedure, ethanolamine 174.1 is protected to give the derivative 174.2. The product is then reacted with a dialkyl alkyl phosphonate 174.3 in which the alkyl group incorporates a leaving group Lv. The alkylation reaction is performed in a polar organic solvent such as acetonitrile or dimethylformamide, in the presence of a strong base such as sodium hydride or lithium hexamethyldisilazide, to afford the

ether product **174.4**. The protecting group is then removed to yield the amine **174.5**. The protection and deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309. The amino compound **174.5** is then coupled, as described in Scheme 1, with the aminoacid **174.6**, to give the amide **174.7**.

For example, equimolar amounts of phthalimide and ethanolamine are reacted in toluene at 70°C, as described in *J. Org. Chem.*, 43, 2320, 1978, to prepare the phthalimido derivative **174.8**, in which Phth is phthalimido. The product is then reacted, in tetrahydrofuran, with sodium hydride and an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate **174.9**, the preparation of which is described in *Tetrahedron Lett.*, 1986, 27, 1497, to afford the ether product **174.10**. The phthalimido group is then removed by treatment of the product **174.10** with ethanolic hydrazine at ambient temperature, as described in *J. Org. Chem.*, 43, 2320, 1978, to yield the amine **174.11**. The product is then coupled, in the presence of dicyclohexylcarbodiimide, with the aminoacid **174.6**, to yield the amide **174.12**.

Using the above procedures, but employing, in place of the methylphosphonate **174.9**, different alkylphosphonates **174.3**, the corresponding products **174.7** are obtained.

Scheme 175 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain incorporating a nitrogen. In this procedure, ethanolamine **174.1** and the aminoacid **174.6** are coupled, as described in Scheme 1, to form the amide **175.1**. The product is then alkylated with a bromoalkyl aldehyde **175.2** to yield the ether **175.3**. The alkylation reaction is performed in a polar organic solvent such as acetonitrile or dioxan, in the presence of a strong base such as potassium tert. butoxide or sodium hydride, at about 60°C. The aldehyde product is then reacted, under reductive amination conditions, as described in Scheme 135, with a dialkyl aminoalkyl phosphonate **175.4**, to produce the amine product **175.5**.

For example, the amide **175.1** is reacted, as described above, with bromoacetaldehyde **175.6**, to afford the ether **175.7**. The product is then reacted in ethanol with a dialkyl aminoethyl phosphonate **175.8**, (Aurora) and sodium triacetoxyborohydride, to yield the amine **175.9**.

Using the above procedures, but employing, in place of the bromoacetaldehyde **175.6**, different bromoalkyl aldehydes **175.2**, and/or different aminoalkyl phosphonates **175.4**, the corresponding products **175.5** are obtained.

Scheme 176 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of a phenyl ring. In this procedure, bromoethylamine 176.1 and the aminoacid 174.6 are coupled, as described in Scheme 1, to afford the amide 176.2. The product is then reacted with the dialkyl hydroxyalkyl-substituted phenylphosphonate 176.3 to prepare the ether 176.4. The alkylation reaction is performed in a polar organic solvent such as dimethyl sulfoxide or dioxan, in the presence of a base such as lithium bis(trimethylsilyl)amide, sodium hydride or lithium piperide.

For example, the amide 176.2 is reacted in dimethylformamide with a dialkyl 4-(2-hydroxyethyl)phenyl phosphonate 176.5, prepared as described in *J. Am. Chem. Soc.*, 1996, 118, 5881, and sodium hydride, to furnish the ether product 176.6.

Using the above procedures, but employing, in place of the hydroxyethyl phenylphosphonate 176.5, different phosphonates 176.3, the corresponding products 176.4 are obtained.

Scheme 177 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain. In this procedure, the aminoacid 174.6 is coupled with a bromoalkoxy-substituted ethylamine 177.1 to give the amide 177.2. The product is then subjected to an Arbuzov reaction with a trialkyl phosphite  $P(OR^1)_3$ . In this procedure, described in *Handb. Organophosphorus Chem.*, 1992, 115, the reactants are heated together at ca. 100°C to afford the product 177.4.

For example, the aminoacid 174.6 is coupled, as described in Scheme 1, in acetonitrile solution containing dicyclohexylcarbodiimide, with 2-bromoethoxyethylamine 177.5, prepared as described in *Vop. Khim. Tekh.*, 1974, 34, 6, to produce the amide 177.6. The product is then heated at 120°C with excess trialkyl phosphite 177.3, to afford the phosphonate 177.7.

Using the above procedures, but employing, in place of the bromoethoxyethylamine 177.5, different bromoalkyl ethylamines 177.1, the corresponding products 177.4 are obtained.

Scheme 178 depicts the preparation of the amines 29.1. The BOC-protected ethanolamine derivatives 178.1, in which the group A is either the substituent link- $P(O)(OR^1)_2$ , or a precursor thereto, prepared as described in Schemes 174 - 177, are deprotected to afford the amines 29.1. The removal of BOC protecting groups is described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example,

hydrogen chloride in ethyl acetate, or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

### Preparation of the chroman phosphonate esters 33.1

Schemes 179 – 181a illustrate the preparation of the chroman phosphonate esters 33.1 which are employed in the preparation of the phosphonate esters 17 and 9.

Scheme 179 depicts the preparation of (2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazol-4-yl)-methanol, 179.6, 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carbaldehyde, 179.7, and 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carboxylic acid, 179.8, which are used in the preparation of the phosphonates 33.1. In this procedure, (2H-chromen-2-yl)-methanol 179.1, prepared as described in *J. Chem. Soc., (D)*, 344, 1973, is converted, as described above, (Scheme 1) into the tert. butyldimethylsilyl ether 179.2. The product is then reacted, as described in *J. Het. Chem.*, 1975, 12, 1179, with silver cyanate and iodine in ether, so as to afford the addition product 179.3. This compound is then heated on methanol to yield the carbamate derivative 179.4. The latter compound is heated in xylene at reflux, as described in *J. Het. Chem.*, 1975, 12, 1179, to produce the oxazoline derivative 179.5. The silyl group is then removed by reaction with tetrabutylammonium fluoride in tetrahydrofuran to yield the carbinol 179.6. The carbinol is oxidized to produce the aldehyde 179.7. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, dimethyl sulfoxide/acetic anhydride or dimethyl sulfoxide-dicyclohexyl carbodiimide. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. The aldehyde 179.7 is oxidized to the carboxylic acid 179.8. The oxidation of aldehydes to carboxylic acids is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 838ff. The conversion is effected by treatment with oxidizing agents such as potassium permanganate, ruthenium tetroxide, chromium trioxide in acetic acid, or, preferably, by the use of silver oxide, as described in *J. Am. Chem. Soc.*, 73, 2590, 1951.

Scheme 180 illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde 179.7 is reacted, under reductive amination conditions, as described in Scheme 175, with a dialkyl aminoalkyl phosphonate 180.1, to give the amine 180.2. The oxazoline group is then

hydrolyzed, for example by reaction with aqueous potassium hydroxide, as described in *J. Het. Chem.*, 1975, 12, 1179, to yield the hydroxyamine **180.3**.

For example, the aldehyde **179.7** is reacted in ethanol with a dialkyl aminomethyl phosphonate **180.4**, (Interchim) and sodium triacetoxyborohydride, to produce the amine **180.5**. The oxazoline is then hydrolyzed, as described above, to afford the hydroxyamine **180.6**.

Using the above procedures, but employing, in place of the aminomethyl phosphonate **180.4**, different phosphonates **180.1**, the corresponding products **180.3** are obtained.

Scheme **181** illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an amide group. In this procedure, the carboxylic acid **179.8** is coupled, as described in Scheme **1**, with a dialkyl aminoalkyl phosphonate **180.1**, to produce the amide **181.1**. Hydrolysis of the oxazoline group, as described above, then yields the hydroxyamine **181.2**.

For example, the carboxylic acid **179.8** is coupled with a dialkyl aminopropyl phosphonate **181.3**, (Acros) to afford the amide **181.4**, which is then hydrolyzed to give the hydroxyamine **181.5**.

Using the above procedures, but employing, in place of the aminopropyl phosphonate **181.3**, different phosphonates **180.1**, the corresponding products **181.2** are obtained.

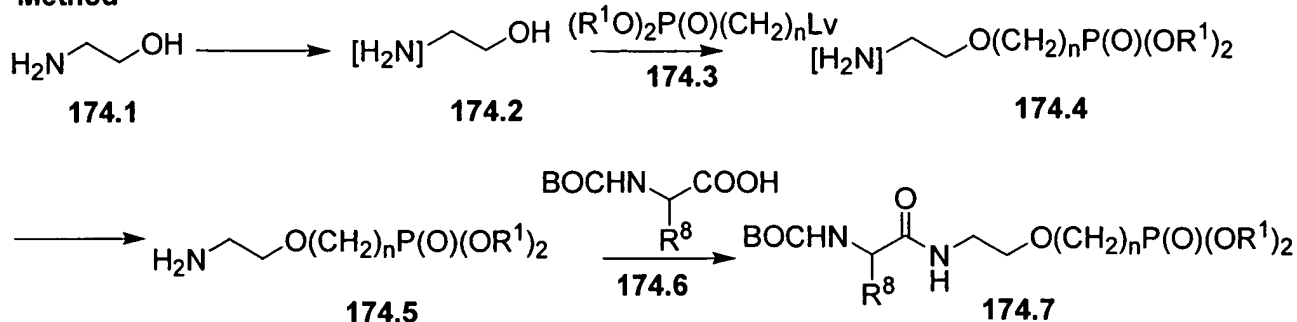
Scheme **181a** illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of a thioalkyl group. In this procedure, the carbinol **179.6** is converted into the bromo derivative **181a.1**. The conversion of alcohols into bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 356ff. For example, the alcohol is reacted with triphenyl phosphine and carbon tetrabromide, trimethylsilyl bromide, thionyl bromide and the like. The bromo compound is then reacted with a dialkyl thioalkyl phosphonate **181a.2** to effect displacement of the bromide and formation of the thioether **181a.3**. The reaction is performed in a polar organic solvent such as ethanol in the presence of a base such as potassium carbonate. Removal of the isoxazoline group then produces the hydroxyamine **181a.4**.

For example, the bromo compound **181a.1** is reacted in ethanol with a dialkyl thioethyl phosphonate **181a.5**, prepared as described in *Zh. Obschei. Khim.*, 1973, 43, 2364, and potassium carbonate, to yield the thioether product **181a.6**. Hydrolysis, as described above, then affords the hydroxyamine **181a.7**.

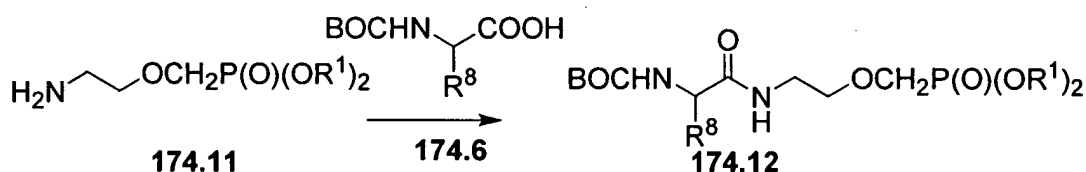
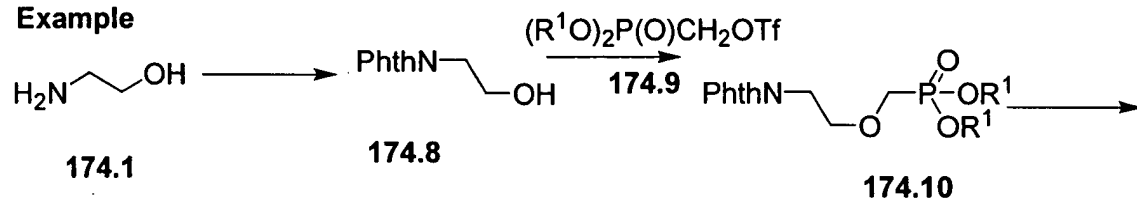
Using the above procedures, but employing, in place of the thioethyl phosphonate **181a.5**, different phosphonates **181a.2**, the corresponding products **181a.4** are obtained.

# Scheme 174

## Method

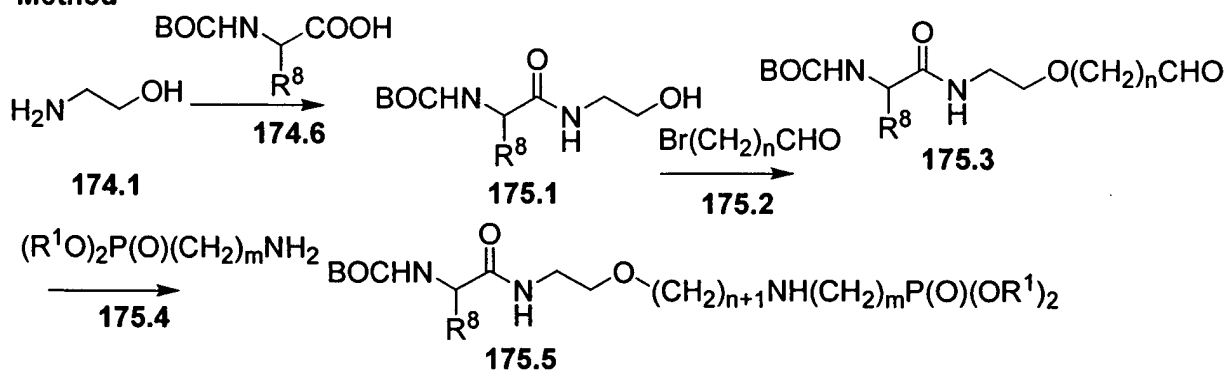


## Example

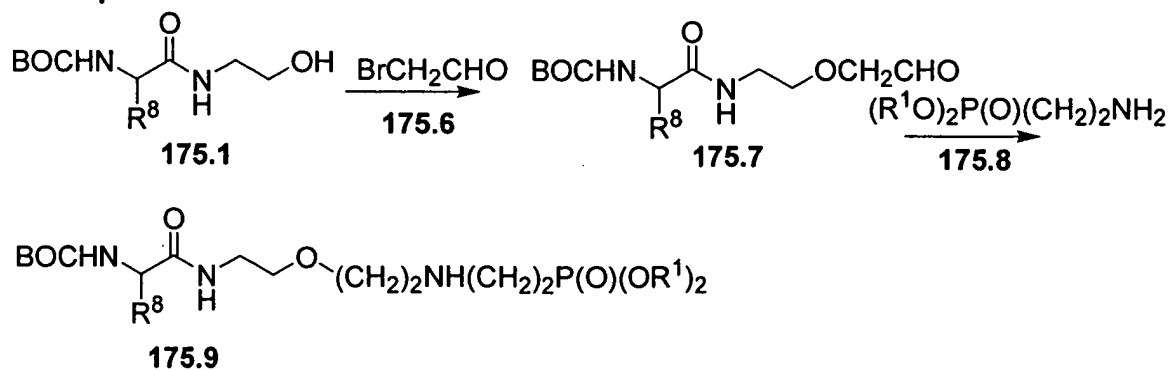


# Scheme 175

## Method

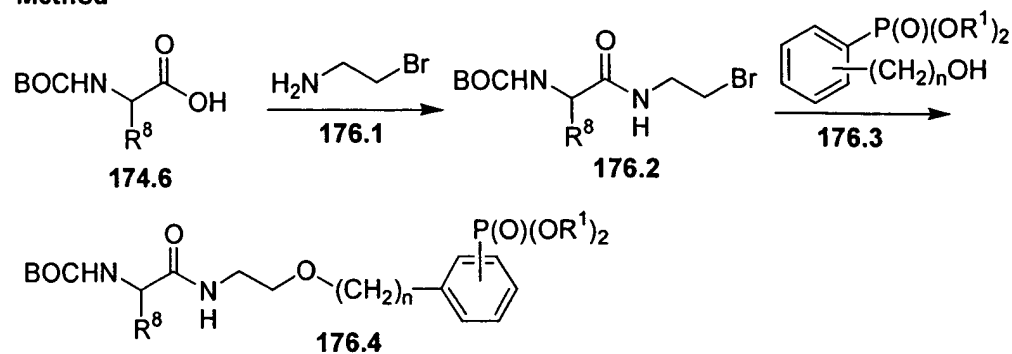


## Example

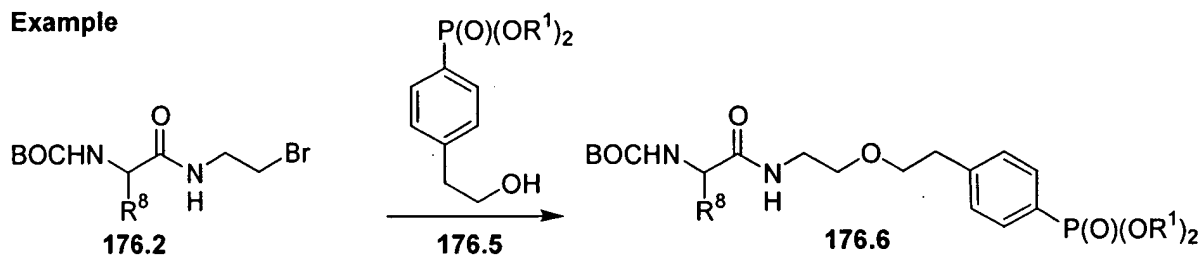


### Scheme 176

#### Method

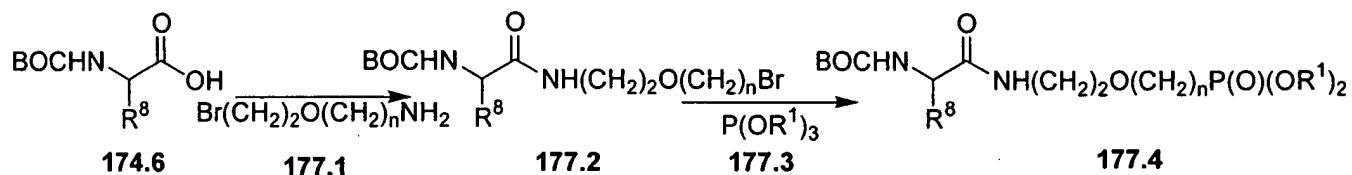


#### Example

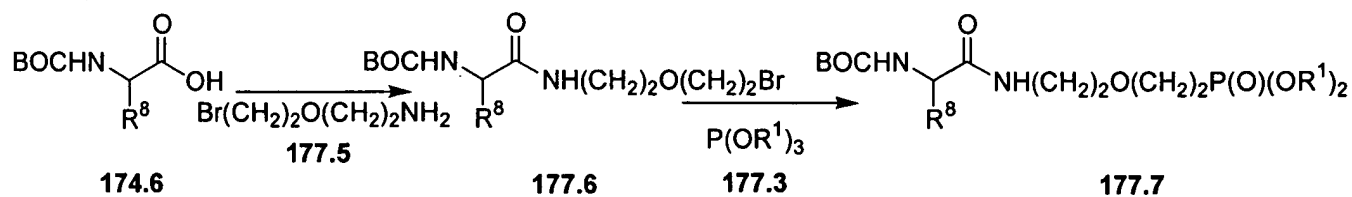


### Scheme 177

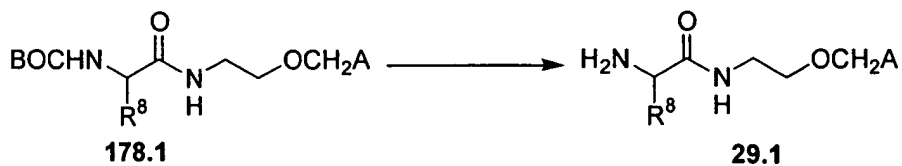
#### Method



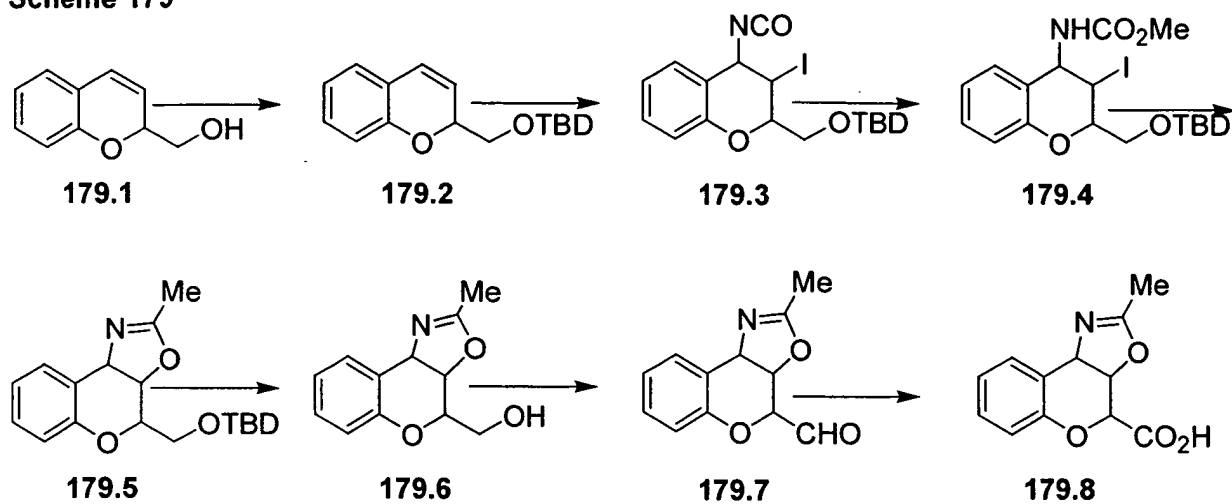
#### Example



### Scheme 178

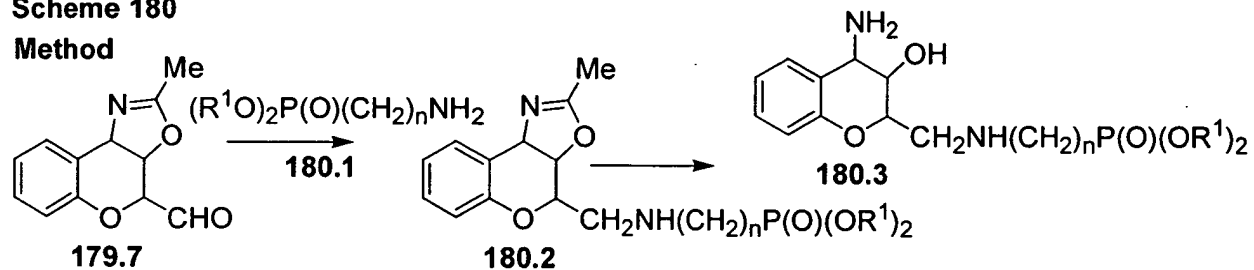


**Scheme 179**

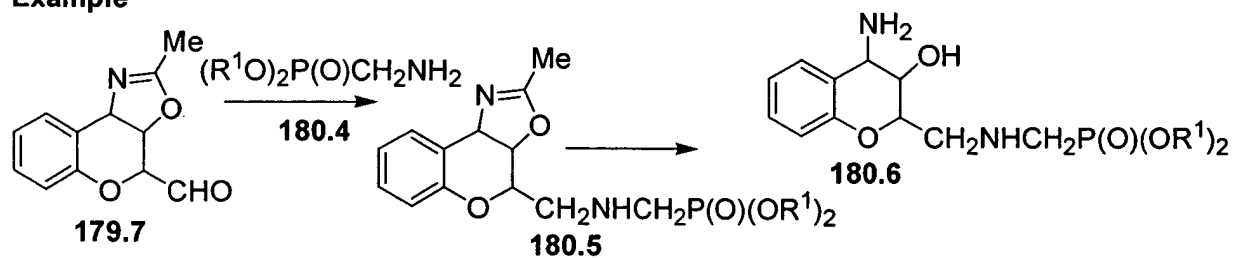


**Scheme 180**

**Method**

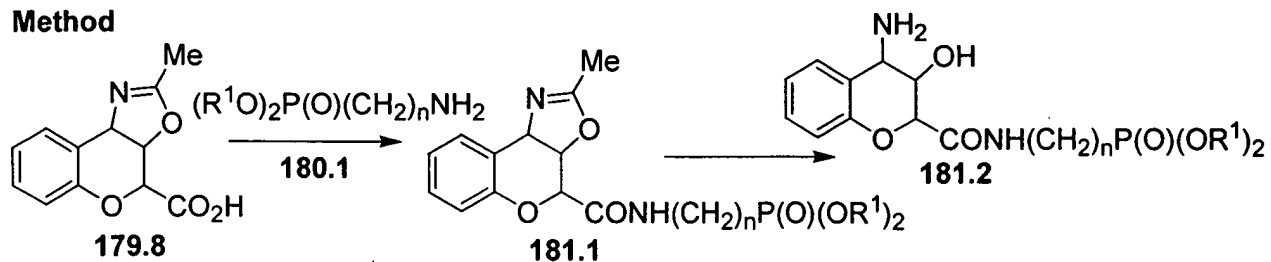


**Example**

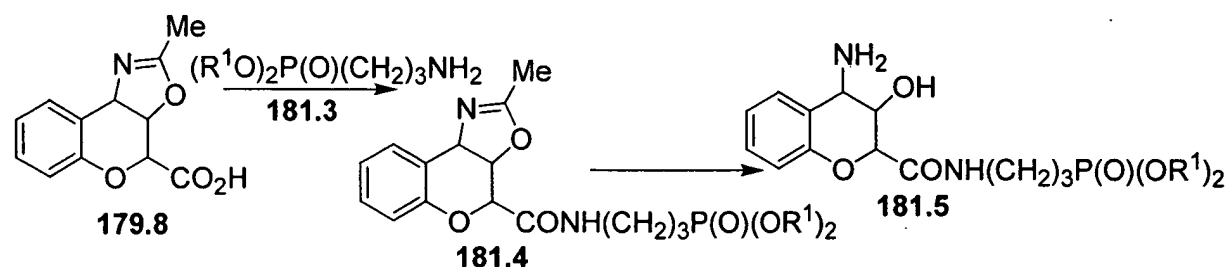


## Scheme 181

### Method

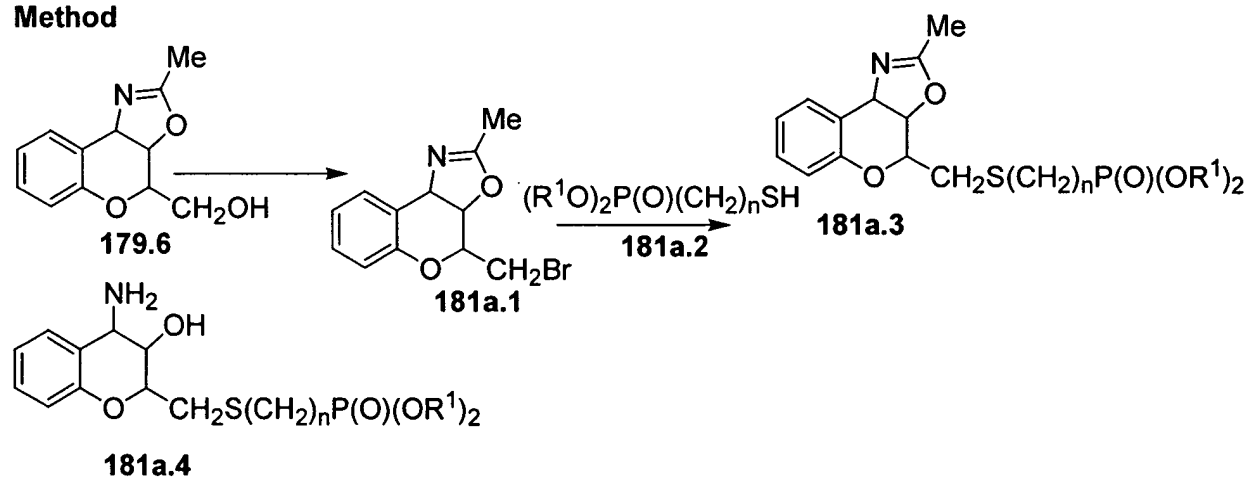


### Example

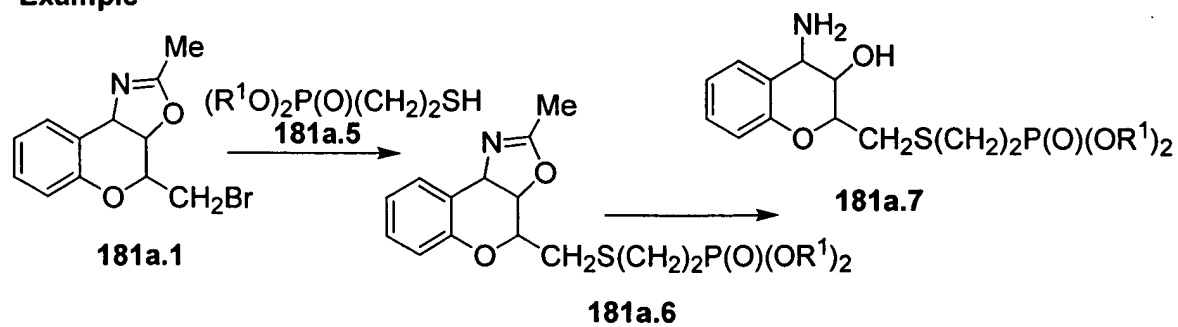


## Scheme 181a

### Method



### Example



### Preparation of phenylalanine derivatives 37.1 incorporating phosphonate moieties

Schemes 182 - 185 illustrate the preparation of phosphonate-containing phenylalanine derivatives 37.1 which are employed in the preparation of the intermediate phosphonate esters 10 and 19.

Scheme 182 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 182.1.

In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester 182.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion is effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 182.2 is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Thiophenols are also protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester 182.3 is then converted into the BOC derivative 182.4. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride, in a solvent such as tetrahydrofuran at ambient temperature, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972. S-Adamantyl groups are removed by treatment with mercuric trifluoroacetate in acetic acid, as described in *Chem. Pharm. Bull.*, 26, 1576, 1978.

The resultant phenol or thiophenol 182.5 is then reacted under various conditions to provide protected phenylalanine derivatives 182.9, 182.10 or 182.11, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **182.5** is reacted with a dialkyl bromoalkyl phosphonate **182.6** to afford the ether or thioether product **182.9**. The alkylation reaction is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **182.9**. Deprotection of the benzyl ester group, for example by means of catalytic hydrogenation over a palladium catalyst, then yields the carboxylic acid **182.12**. The benzyl esters **182.10** and **182.11**, the preparation of which is described above, are similarly deprotected to produce the corresponding carboxylic acids.

For example, as illustrated in Scheme **182**, Example **1**, a hydroxy-substituted phenylalanine derivative such as tyrosine, **182.13** is converted, as described above, into the benzyl ester **182.14**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972, to afford the silyl ether **182.15**. This compound is then converted, as described above, into the BOC derivative **182.16**. The silyl protecting group is removed by treatment of the silyl ether **182.16** with a tetrahydrofuran solution of tetrabutylammonium fluoride at ambient temperature, as described in *J. Am. Chem. Soc.*, 94, 6190, 1972, to afford the phenol **182.17**. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **182.18** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **182.19**. Debenzylation then produces the carboxylic acid **182.20**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.13**, different hydroxy or thio-substituted phenylalanine derivatives **182.1**, and/or different bromoalkyl phosphonates **182.6**, the corresponding ether or thioether products **182.12** are obtained.

Alternatively, the hydroxy or mercapto-substituted phenylalanine derivative **182.5** is reacted with a dialkyl hydroxymethyl phosphonate **182.7** under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds **182.10**. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or

thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **182.10**.

For example, as shown in Scheme **182**, Example **2**, 3-mercaptophenylalanine **182.21**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **182.22**. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in *Bull. Chem. Soc. Jpn.*, 37, 433, 1974, to afford the 4-methoxybenzyl thioether **182.23**. This compound is then converted into the BOC-protected derivative **182.24**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **182.24** with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in *J. Org. Chem.*, 52, 4420, 1987, to afford the thiol **182.25**. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate **182.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in *Synthesis*, 4, 327, 1998, to yield the thioether product **182.26**. The benzyl ester protecting group is then removed to afford the carboxylic acid **182.27**.

Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **182.21**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or different dialkyl hydroxymethyl phosphonates **182.7**, the corresponding products **182.10** are obtained.

Alternatively, the hydroxy or mercapto-substituted protected phenylalanine derivative **182.5** is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **182.8** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **182.11**.

For example, as illustrated in Scheme **182**, Example **3**, 3-hydroxyphenylalanine **182.28** (Fluka) is converted, using the procedures described above, into the protected compound **182.29**. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **182.30**, prepared as described in *Tetrahedron Lett.*, 1986, 27, 1477, to afford the ether product **182.31**. Debenzylation then produces the carboxylic acid **182.32**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.28**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or different dialkyl trifluoromethanesulfonyloxymethylphosphonates **182.8**, the corresponding products **182.11** are obtained.

Scheme **183** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted protected phenylalanine derivative **183.3** and a dialkyl aminoalkylphosphonate **183.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **183.1** is converted, as described above, into the BOC protected benzyl ester **183.2**. The latter compound is then oxidized to afford the corresponding aldehyde **183.3**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **183.3**. For example, the carbinol **183.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in *J. Org. Chem.*, 43, 2480, 1978, to yield the aldehyde **183.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **183.4** in the presence of a suitable reducing agent to afford the amine product **183.5**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The benzyl protecting group is then removed to prepare the carboxylic acid **183.6**.

For example, 3-(hydroxymethyl)-phenylalanine **183.7**, prepared as described in *Acta Chem. Scand. Ser. B*, 1977, B31, 109, is converted, as described above, into the formylated derivative **183.8**. This compound is then reacted with a dialkyl aminoethylphosphonate **183.9**, prepared as described in *J. Org. Chem.*, 200, 65, 676, in the presence of sodium

cyanoborohydride, to produce the alkylated product **183.10**, which is then deprotected to give the carboxylic acid **183.11**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **183.7**, different hydroxymethyl phenylalanines **183.1**, and/or different aminoalkyl phosphonates **183.4**, the corresponding products **183.6** are obtained.

Scheme **184** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **184.1** is converted, as described above, (Scheme **182**) into the protected derivative **184.2**. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **184.3** to produce the phosphonate ester **184.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. The product is then deprotected to afford the carboxylic acid **184.5**.

For example, 3-bromophenylalanine **184.6**, prepared as described in *Pept. Res.*, 1990, 3, 176, is converted, as described above, (Scheme **182**) into the protected compound **184.7**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **184.8**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the phosphonate product **184.9**. Debenzylation then yields the carboxylic acid **184.10**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **184.6**, different bromophenylalanines **184.1**, and/or different dialkylphosphites **184.3**, the corresponding products **184.5** are obtained.

Scheme **185** depicts the preparation of the aminoacid derivative **37.1** which is employed in the preparation of the phosphonate esters **10** and **19**. In this procedure, the BOC-protected phenylalanine derivatives **185.1**, in which the substituent A is the group link-P(O)(OR<sup>1</sup>)<sub>2</sub> or a precursor group, the preparation of which is described in Schemes **182** – **184**, is converted into the esters or amides **185.2** in which R<sup>9</sup> is morpholino or alkoxy. The transformation is accomplished by coupling the acid, as described in Scheme **1**, with morpholine or an alkanol in the presence of a carbodiimide. The product **185.2** is then deprotected to afford the free amine **185.3**, for example as described in Scheme **3**. The amine **185.3** is then coupled, as described in

Scheme 1, with the aminoacid **174.6**, to give the amide **185.4**. The BOC group is then removed, as described in Scheme 49, to produce the amine **37.1**.

#### **Preparation of the dimethoxyphenylpropionic esters 21.1 incorporating phosphonate groups**

Scheme 186 illustrates the preparation of the dimethoxyphenylpropionic acid derivatives **21.1** which are employed in the preparation of the phosphonate esters **6**. In this procedure, the dimethoxybenzyl alcohol derivative **186.1**, in which the substituent A is the group link- $\text{P}(\text{O})(\text{OR}^1)_2$  or a precursor group, the preparation of which is described in Schemes 165 – 168, is converted into the corresponding aldehyde **186.2**. The oxidation is effected as described in Scheme 175. The aldehyde is then subjected to a Wittig reaction with methyl triphenylphosphoranylideneacetate **138.2**, as described in Scheme 138, to generate the cinnamic ester derivative **186.3**. The double bond is then reduced, as described in Scheme 138, to afford the phenylpropionic ester **21.1**. Alternatively, the dimethoxybenzyl bromide derivative **186.4**, the preparation of which is described in Scheme 169, is reacted, as described in Scheme 138, with dimethyl malonate **186.5** to yield the malonic ester derivative **186.6**, which is then transformed, as described in Scheme 138, into the ester **21.1**.

#### **Preparation of the phosphonate-containing benzyl iodides 58.1 and benzylcarbamates 125.3**

Schemes 187 - 191 illustrate methods for the preparation of the benzyl iodide derivatives **58.1** which are employed in the synthesis of the phosphonate esters **14**, and of the benzyl carbamates **125.3** which are employed in the preparation of the phosphonate esters **22**.

Scheme 187 illustrates the preparation of benzaldehyde phosphonates **187.3** in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde **187.1** is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate **187.2**, under reductive amination conditions, as describe above in Scheme 135, to yield the phosphonate product **187.3**.

For example, benzene-1,3-dialdehyde **187.4** is reacted with a dialkyl aminopropyl phosphonate **187.5**, (Acros) and sodium triacetoxyborohydride, to afford the product **187.6**.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde **187.4**, different benzene dialdehydes **187.1**, and/or different phosphonates **187.2**, the corresponding products **187.3** are obtained.